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MOST RECENT DERWENT UPDATE:     200315        <200315/DW>
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=> d all abeq tech abex tot

L74  ANSWER 1 OF 5  WPIX (C) 2003 THOMSON DERWENT
AN   2000-224559 [19]   WPIX
CR   1999-229135 [19]; 1999-254253 [21]; 2000-224558 [19]
DNC  C2000-068643
TI   Bioreductive drug conjugates, useful for treating various conditions
     according to the medicament e.g. anti-infectives or for treating
     conditions associated with hypoxia and/or ischemia.
DC   B03 B05
IN   FREEMAN, S; JAFFER, M; STRATFORD, I
PA   (THER-N) THERAMARK LTD; (UYMA-N) UNIV VICTORIA
     MANCHESTER
CYC  89
PI   WO 2000010611 A2 20000302 (200019)* EN   45p    A61K047-48      <--
        RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL
            OA PT SD SE SL SZ UG ZW
         W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES
            FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS
            LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ
            TM TR TT UA UG US UZ VN YU ZA ZW
     AU 9954308    A  20000314 (200031)             A61K047-48      <--
     EP 1104408    A2 20010606 (200133)  EN         C07D233-91      <--
         R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
            RO SE SI
     JP 2002523382 W  20020730 (200264)       44p    A61K047-48      <--
ADT  WO 2000010611 A2 WO 1999-GB2620 19990819; AU 9954308 A AU
     1999-54308 19990819; EP 1104408 A2 EP 1999-940311 19990819,
     WO 1999-GB2620 19990819; JP 2002523382 W WO 1999-GB2620
```

19990819, JP 2000-565931 19990819

FDT AU 9954308 A Based on WO 200010611; EP 1104408 A2 Based on WO 200010611; JP 2002523382 W Based on WO 200010611

PRAI **GB 1998-18156 19980820; GB 1998-18030 19980819**

IC ICM **A61K047-48; C07D233-91**

ICS **A61K031-04**; A61K031-415; A61K045-00; A61P001-02; A61P001-04; A61P001-16; A61P003-10; A61P009-10; A61P009-12; A61P013-12; A61P017-06; A61P025-28; A61P029-00; A61P031-04; A61P035-00; A61P037-00; **C07C205-06; C07D233-92; C07D233-94; C07D233-95**

AB WO 200010611 A UPAB: 20021105

NOVELTY - A bioreductive conjugate comprising a bioreductive moiety incorporating an aromatic ring substituted with a **nitro** group, linked to at least 1 therapeutic agent, is used to target therapeutic agent to localized regions of hypoxic and/or ischemic tissue.

DETAILED DESCRIPTION - A bioreductive conjugate comprises a bioreductive moiety incorporating an aromatic ring substituted with a **nitro** group, linked to at least 1 therapeutic agent, where bioreduction of the **nitro** group causes release of the therapeutic agent by a through bond elimination and the residue of the bioreductive moiety undergoes an intramolecular cyclization reaction in which the **nitrogen** of the original **nitro** group provides an atom of the ring.

USE - Conjugates in which the therapeutic agent is an anti-infective (e.g. antibiotic or antiviral agent), analgesic, anaesthetic, antiinflammatory or anti-neoplastic agent are claimed. Also claimed is the use of the bioreductive conjugates for treating conditions associated with hypoxia and/or ischemia, e.g. inflammatory conditions, diabetes, atherosclerosis, stroke, sepsis, Alzheimer's disease and other neurological diseases, cancer, kidney disease, digestive diseases, liver disease, chronic periodontitis and ischemia following tissue transplantation, particularly rheumatoid arthritis and osteoarthritis, an inflammatory condition of soft tissue, a gastrointestinal disorder, e.g. Crohn's disease, healing of wounds and treating fibrotic disorders, ulcerative colitis, inflammatory bowel disease, epilepsy, cardiovascular reperfusion injury, cerebral reperfusion injury, hypertension, cystic fibrosis, psoriasis, para-psoriasis, peptic ulcer, gastric ulcer, duodenal ulcer, diabetic ulcer, dementia oncology and AIDS.

Dwg.0/0

FS CPI

FA AB; DCN

MC CPI: B05-B01E; B05-B01F; B05-B01M; B05-B01N; B07-D09; B07-H; B10-A09A; B10-B01; B10-B02F; B10-B02G; B10-B03; B10-B04B; B10-D03; B10-E02; B10-E04B; B10-E04C; B10-G02; **B10-G03**; B14-A01; B14-A02B1; B14-C01; B14-C03; B14-C07; B14-C08; B14-C09; B14-E08; B14-E10C; B14-F02B; B14-F02D; B14-F05; B14-F07; B14-H01; B14-J01A4; B14-J07; B14-K01; B14-N06B; B14-N10; B14-N12; B14-N17B; B14-N17C; B14-S04; B14-S06

TECH UPTX: 20000419

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Compounds: The conjugate is preferably of formula (I) or (II):

Ar = an optionally substituted aromatic ring system;

Drug = a therapeutic agent;

X = a linker, which may be part of the drug, e.g. O, NH, S or an alcohol;

R1-R4 = H, optionally substituted alkyl, aryl, halo, NH2, alkoxy, ether, ester, alcohol, phenol, NO2, amide, thiol, sulfate, phosphate or phosphonate;

n = 1-3.

The reaction scheme for drug release from (I) and intramolecular cyclization (disclosed) is e.g. as shown below:

Q = H or OH.

Preferred Compounds:

Ar = the atoms required to complete a 4-**nitro**-2-R1-imidazol-5-yl group or a 2-**nitro**-phenyl substituted by groups R1-R4.
Other disclosed possible Ar groups are pyrrole, thiophene, furan, oxazole, thiazole, and tetrazole all optionally substituted by R1-R4.
The bioreductive moiety is non cytotoxic.

ABEX
ADMINISTRATION - Administration is by conventional routes. Daily dosage is 0.01-20 mg/kg.

L74 ANSWER 2 OF 5 WPIX (C) 2003 THOMSON DERWENT
AN 2000-224558 [19] WPIX
CR 1999-229135 [19]; 1999-254253 [21]; 2000-224559 [19]
DNC C2000-068642
TI Bioreductive conjugate useful for treating, e.g. fibrotic disorders, ulcerative colitis, psoriasis and peptic ulcers.
DC **B05**
IN ADAMS, G; BLAKE, D; NAUGHTON, D; **STRATFORD, I**
PA (ADAM-I) ADAMS M; (THER-N) **THERAMARK LTD**
CYC 88
PI WO 2000010610 A2 20000302 (200019)* EN 46p A61K047-48 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW
AU 9954296 A 20000314 (200031) A61K047-48 <--
ADT WO 2000010610 A2 **WO 1999-GB2606 19990819**; AU 9954296 A **AU 1999-54296 19990819**
FDT AU 9954296 A Based on WO 200010610
PRAI **GB 1998-18156 19980820; GB 1998-18027 19980819**
IC ICM **A61K047-48**
AB WO 200010610 A UPAB: 20000630
NOVELTY - Use of bioreductive conjugate (BC) comprising non-cytotoxic bioreductive moiety (BM) linked to a therapeutic agent (TA) is new.
DETAILED DESCRIPTION - The use of BC comprising a non-cytotoxic BM with at least one TA linked to it, for healing of wounds and the treatment of fibrotic disorders, ulcerative colitis, inflammatory bowel disease, epilepsy, cardiovascular reperfusion injury, cerebral reperfusion injury, hypertensions, cystic fibrosis, psoriasis, para-psoriasis, peptic ulcers, gastric ulcers, duodenal ulcers, diabetic ulcers, dementia, oncology and AIDS.
INDEPENDENT CLAIMS are also included for the following:
(1) use of BC for the treatment of rheumatoid arthritis, where BC comprises a non-cytotoxic BM with TA selected from sulfasalazine, mesalazine, penicillamine, azathioprine, chlorambucil, myochrysine (sodium auro thiomalate), hydroxychloroquine, methotrexate, cyclosporin myocrisin and neoral, linked to it;
(2) use of BC for the treatment of diabetes, where BC comprises a non-cytotoxic BM with at least one TA selected from a carbose, aspirin, indomethacin, capropril and prostaglandin synthetase inhibitors, linked to it;
(3) use of BC for the treatment of ischemia, where BC comprises BM with at least one TA selected from inositol nicotinate, calcium antagonists such as niphedipine and verapamil; anti-platelets, such as aspirin and dipyridamole, ACE inhibitors, e.g. ramapril and trandolapril and fibrinolytic agents, linked to it;
(4) BC comprising BM with ibuprofen, naproxen, fenoprofenb, benoxaprofen, sulinadac, indomethacin, tolmetin or diclofenac, linked to it;
(5) BC comprising BM with a PDE-4 or PDE-5 inhibitor linked to it;
(6) use of BC for the treatment of a hypoxic condition, where BC comprises BM with a PDE inhibitor linked to it, and

(7) BC comprising BM with an immunosuppressive, cell cycle specific drug, cell cycle non-specific drug, metalloprotease inhibitor or inhibitor of nitric oxide synthase, linked to it.

ACTIVITY - Vulnerary; Gastrointestinal-Gen.; Anticonvulsant; Hypotensive; Respiratory-Gen.; Antipsoriatic; Antiulcer; Nootropic; Neuroprotective; Anti-HIV; Antirheumatic; Antiarthritic; Antidiabetic; Cerebroprotective; Cytostatic. A549 lung cancer cells were exposed to TMK-209 for three hours in both aerobic and hypoxic conditions. TMK209 exhibited IC50 values of 116 um and 37 um in air and N2, respectively and is capable of undergoing self-alkylation. formula

MECHANISM OF ACTION - TGF-Antagonist-Beta-1; TGF-Antagonist-Beta-2; Interferon-Antagonist-Gamma; Interleukin-Antagonist-6; Interferon-Agonist-Gamma; Activin-Agonist; Inhibin-Agonist.

USE - The bioreductive conjugates are useful for treating fibrotic disorders, ulcerative olitis, inflammatory bowel disease, epilepsy, cardiovascular reperfusion injury, cerebral reperfusion injury, hypertension, cystic fibrosis, psoriasis, para-psoriasis, peptic ulcers, gastric ulcers, duodenal ulcers, diabetic ulcers, dementia, oncology, AIDS, rheumatoid arthritis, diabetes, ischemia, and hypoxic conditions (claimed).

ADVANTAGE - The conjugate is such that after release of the therapeutic agent the bioreductive moiety is itself a stable non-cytotoxic species or reacts with itself to form a stable, non-cytotoxic species. This minimises direct interaction of the carrier with DNA or other biomolecules thus avoiding potential mutagenic side effects.

Dwg.0/0

FS CPI

FA AB; DCN

MC CPI: B01-B02; B04-C01C; B04-C02X; B04-H02A; B04-H02D; B04-H02L; B04-H06B; B05-A01B; B06-D01; B06-D02; B06-D05; B06-D09; B06-E02; B07-D02; B07-D04C; B07-D09; B10-A15; B10-B02A; B10-B02B; B10-C04D; B10-C04E; B14-C06; B14-C09; B14-E08; B14-E10; B14-F02B; B14-G01B; B14-H01B; B14-J01A4; B14-J07; B14-K01; B14-N16; B14-N17B; B14-N17C; B14-S04

TECH UPTX: 20000419

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Method The therapeutic agent is a growth factor neutralising agent or agent specific against only fibrotic growth factors eg. TGF-beta 1, TGF-beta 2, PDGF, IFN gamma or IL-1. Alternatively, the therapeutic agent is a non-fibrotic growth factor eg. TGF-beta 3, FGF-1, FGF-2, IL-4 or IL-10. Alternatively, the therapeutic agent is a soluble betaglycan or its fragment or analog, an inhibitor of Interferon-gamma, a stimulator of IFN-gamma, an inhibitor of activation of at least one integrin receptor, an inhibitor of at least one convertase enzyme, a stimulator of activin and/or inhibin, one which modulates actin assembly and organisation, an IL-6 inhibitor, latency associated peptide or its functional analog, insulin like growth factor II or its functional analog, or a compound that influences the sex hormone system.

ABEX

SPECIFIC COMPOUNDS - The therapeutic agent is eg. sulphasalazine, metronidazole, cyclosporin A, phenytoin, omeprazole, ibuprofen or prednisolone.

ADMINISTRATION - Dosage is 0.05-10 mg/kg/day administered, e.g. orally, parenterally, rectally or topically.

L74 ANSWER 3 OF 5 WPIX (C) 2003 THOMSON DERWENT

AN **1996-239187** [24] WPIX

DNC **C1996-076279**

TI Accelerated healing of skin wounds - by topical admin. of an adduct of nitric oxide and a polymer..

DC A96 B04

IN PULFER, S; SHABANI, M; SMITH, D J

PA (UYAK) UNIV AKRON

CYC 65
PI WO 9613164 A1 19960509 (199624)* EN 28p A01N043-04
RW: AT BE CH DE DK ES FR GB GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG
W: AM AT AU BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU IS JP KE KG KP KR KZ LK LR LT LU LV MD MG MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TT UA UG UZ VN
US 5519020 A 19960521 (199626) 12p A61K031-54
AU 9539715 A 19960523 (199635) A01N043-04
NO 9701926 A 19970610 (199734) A61K031-715
EP 788308 A1 19970813 (199737) EN A01N043-04
R: DE DK ES FR GB IT NL SE
AU 688627 B 19980312 (199822) A01N043-04
MX 9703084 A1 19970701 (199827) A01N043-04
JP 10508305 W 19980818 (199843) 29p A61K031-785
KR 97706731 A 19971201 (199847) A01N043-04
MX 199394 B 20001103 (200215) A61K031-04 <--
NO 313863 B1 20021216 (200307) A61K031-715
ADT WO 9613164 A1 WO 1995-US14071 19951030; US 5519020 A US 1994-330596 19941028; AU 9539715 A AU 1995-39715 19951030; NO 9701926 A WO 1995-US14071 19951030, NO 1997-1926 19970425; EP 788308 A1 EP 1995-937679 19951030, WO 1995-US14071 19951030; AU 688627 B AU 1995-39715 19951030; MX 9703084 A1 MX 1997-3084 19970428; JP 10508305 W WO 1995-US14071 19951030, JP 1996-514819 19951030; KR 97706731 A WO 1995-US14071 19951030, KR 1997-702805 19970428; MX 199394 B MX 1997-3084 19970428; NO 313863 B1 WO 1995-US14071 19951030, NO 1997-1926 19970425
FDT AU 9539715 A Based on WO 9613164; EP 788308 A1 Based on WO 9613164; AU 688627 B Previous Publ. AU 9539715, Based on WO 9613164; JP 10508305 W Based on WO 9613164; KR 97706731 A Based on WO 9613164; NO 313863 B1 Previous Publ. NO 9701926
PRAI US 1994-330596 19941028
REP 1.Jnl.Ref
IC ICM A01N043-04; **A61K031-04**; A61K031-54; A61K031-715; A61K031-785
ICS **A61K047-48**; A61L015-00; A61P017-02
AB WO 9613164 A UPAB: 19970410
Process for accelerated healing of skin wounds comprises topical admin. of a water-insol. NO-polymer adduct (I) which releases therapeutic amts. of NO in an aq. environment.

Also claimed are the adducts (I) per se, the NO being chemically bonded.

Pref., (I) are non-toxic, the NO is delivered in therapeutic amts. over at least 3 weeks, and when all the NO has been delivered, the insol. polymer (II) is biocompatible. (I) has a halflife of at least 960 mins. Pref., (II) is polyethylene cellulose or poly(ethylene diamine-co-1,4-butanediglycidyl ether). Adducts (I) pref. also comprise an absorbent dressing which is polyisobutylene (low and high mol.wt.), gelatin, pectin, carboxymethyl cellulose, silica, cotton fibres, and polymer compsns. which are water-swellable, water-insol., hydrolytically labile, cross-linked polysaccharides (III) in the form of microparticles.

USE - The adducts provide accelerated healing of skin wounds.

ADVANTAGE - Adducts (I) are stable and do not migrate away from the wound in contrast to known sol. complexes.

Dwg.0/4
FS CPI
FA AB; DCN
MC CPI: A10-E01; A12-V01; A12-V03A; B04-A08C2; B04-A09H; B04-C02; B04-C02A; B04-C02A2; B04-C03B; B04-C03C; B04-N02; B14-N17B
ABEQ US 5519020 A UPAB: 19960705
A process for the accelerated healing of skin wounds which comprises the step of topically adding a water insoluble nitric oxide polymer adduct which releases therapeutic amounts of nitric oxide in an aqueous environment to a surface of the wound.

Dwg.0/4

L74 ANSWER 4 OF 5 WPIX (C) 2003 THOMSON DERWENT
AN **1995-215055** [28] WPIX
CR 1995-206721 [27]; 1995-206866 [27]; 1998-051552 [05]
DNC **C1995-099421**
TI New **nitrogen**-contg. amphiphilic cpds. - useful as carriers for, e.g., antibiotics or nucleic acids.
DC B03 B04 B07 D16
IN HEATH, T D; SOLODIN, I
PA (MEGA-N) MEGABIOS CORP; (VALE-N) VALENTIS INC
CYC 58
PI WO 9514380 A1 19950601 (199528)* EN 33p A01N025-26 <--
RW: AT BE CH DE DK ES FR GB GR IE IT KE LU MC MW NL OA PT SD SE SZ
W: AM AT AU BB BG BR BY CA CH CN CZ DE DK ES FI GB GE HU JP KE KG KP KR KZ LK LT LU LV MD MG MN MW NL NO NZ PL PT RO RU SD SE SI SK TJ TT UA UZ VN
AU 9510999 A 19950613 (199539) A01N025-26 <--
NO 9602073 A 19960709 (199637) C07D000-00 <--
EP 730404 A1 19960911 (199641) EN A01N025-26 <--
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
EP 730404 A4 19970219 (199728) A01N025-26 <--
JP 09505594 W 19970603 (199732) 26p C07D233-64 <--
US 5705655 A 19980106 (199808) 14p C07D233-14 <--
US 5736395 A 19980407 (199821) 8p C12N001-00 <--
NZ 276645 A 19980527 (199827) C07D233-26 <--
AU 691217 B 19980514 (199831) A01N025-26 <--
NO 305557 B1 19990621 (199931) C07D233-18 <--
JP 2918693 B2 19990712 (199933) 10p C07D233-64 <--
CA 2176713 C 20000222 (200029) EN C12N015-88
KR 246839 B1 20000801 (200131) C07D233-08 <--
ADT WO 9514380 A1 **WO 1994-US13363 19941117**; AU 9510999 A **AU 1995-10999 19941117**; NO 9602073 A **WO 1994-US13363 19941117, NO 1996-2073 19960521**; EP 730404 A1 **WO 1994-US13363 19941117, EP 1995-901947 19941117**; EP 730404 A4 EP 1995-901947 ; JP 09505594 W **WO 1994-US13363 19941117, JP 1995-515155 19941117**; US 5705655 A **CIP of US 1992-991935 19921217, CIP of US 1993-157727 19931124, US 1994-247963 19940524**; US 5736395 A **CIP of US 1992-991935 19921217, CIP of US 1993-157727 19931124, Div ex US 1994-247963 19940524, US 1997-858571 19970519**; NZ 276645 A **NZ 1994-276645 19941117, WO 1994-US13363 19941117**; AU 691217 B **AU 1995-10999 19941117**; NO 305557 B1 **WO 1994-US13363 19941117, NO 1996-2073 19960521**; JP 2918693 B2 **WO 1994-US13363 19941117, JP 1995-515155 19941117**; CA 2176713 C **CA 1994-2176713 19941117, WO 1994-US13363 19941117**; KR 246839 B1 **WO 1994-US13363 19941117, KR 1996-702744 19960523**
FDT AU 9510999 A Based on WO 9514380; EP 730404 A1 Based on WO 9514380; JP 09505594 W Based on WO 9514380; NZ 276645 A Based on WO 9514380; AU 691217 B Previous Publ. AU 9510999, Based on WO 9514380; NO 305557 B1 Previous Publ. NO 9602073; JP 2918693 B2 Previous Publ. JP 09505594, Based on WO 9514380; CA 2176713 C Based on WO 9514380
PRAI **US 1994-247963 19940524; US 1993-157727 19931124 ; US 1992-991935 19921217; US 1997-858571 19970519**
REP 01Jnl.Ref; US 5264618; No-Citns.
IC ICM A01N025-26; C07D000-00; **C07D233-08; C07D233-14; C07D233-18; C07D233-26; C07D233-64**; C12N001-00; C12N015-88
ICS A01N025-28; A01N043-04; A61K009-127; A61K031-415; A61K031-70; A61K047-22; **A61K047-48; C07D233-22; C07D233-60**; C12N001-20; C12N015-00; C12N015-09

ICA A61K048-00; C12N005-10
AB WO 9514380 A UPAB: 20010607
The following are claimed: (A) **nitrogen**-contg. amphiphiles of formula (I), where R, R1 = a straight chain, aliphatic hydrocarbyl gp. contg. 11-29C; (B) transformation of cells, comprising contacting the cells with a plurality of complexes comprising an expression cassette and a cpd. (I); the complexes provide for transmission of cells in at least 1 tissue of a mammal, and are susceptible to endogenous enzymatic cleavage to non-toxic prods.; and (C) synthesis of imidazolinium ions, comprising heating a precursor cpd. of formula (II) in an organic solvent at a temp. above the b.pt. of water, where R(a), R1, = organic gps. which render (II) soluble in the solvent and which are stable to reaction in the solvent at the reaction temp.
USE - (I) are useful as carriers for various biological molecules such as antibiotics or nucleic acids. They may be used in formulations for prepn. of lipid vesicles or liposomes for use in intracellular delivery systems (e.g. for transfection procedures as described above). Admin. of (I) complexed to the biological molecule is, e.g., topical, parenteral or by inhalation.
ADVANTAGE - The cpds. (I) are non-toxic to hosts, even after repeated admin.
Dwg.0/0
FS CPI
FA AB; GI; DCN
MC CPI: B07-D09; D05-H10; D05-H19
ABEQ US 5705655 A UPAB: 19980223
The following are claimed: (A) **nitrogen**-contg. amphiphiles of formula (I), where R, R1 = a straight chain, aliphatic hydrocarbyl gp. contg. 11-29C; (B) transformation of cells, comprising contacting the cells with a plurality of complexes comprising an expression cassette and a cpd. (I); the complexes provide for transmission of cells in at least 1 tissue of a mammal, and are susceptible to endogenous enzymatic cleavage to non-toxic prods.; and (C) synthesis of imidazolinium ions, comprising heating a precursor cpd. of formula (II) in an organic solvent at a temp. above the b.pt. of water, where R(a), R1, = organic gps. which render (II) soluble in the solvent and which are stable to reaction in the solvent at the reaction temp.
USE - (I) are useful as carriers for various biological molecules such as antibiotics or nucleic acids. They may be used in formulations for prepn. of lipid vesicles or liposomes for use in intracellular delivery systems (e.g. for transfection procedures as described above). Admin. of (I) complexed to the biological molecule is, e.g., topical, parenteral or by inhalation.
ADVANTAGE - The cpds. (I) are non-toxic to hosts, even after repeated admin.
Dwg.0/0

L74 ANSWER 5 OF 5 WPIX (C) 2003 THOMSON DERWENT
AN **1990-328178** [44] WPIX
DNN **N1990-251194** DNC **C1990-142494**
TI New conjugate - comprising poly alcohol, active agent, linker and protein is useful as tumour marker.
DC B03 B04 B05 K08 S03
IN FRIEDRICH, E; GRASCHEW, G; MAIERBORST, W; SCHRENK, H J; SINN, H; WOHRLE, D; MAIER-BORST, W; SCHRENK, H; WOEHRLE, D; WOERHLE, D
PA (FARH) HOECHST AG; (DEKR-N) DEUT KREBSFORSCHUNGSZENT; (DEKR-N) DEUT KREBSFORSCHUNGSZENTRUM; (DEKR-N) DEUT KREBSFORSCHUNGSINSTITUT
CYC 16
PI DE 3912792 A 19901025 (199044)* <--
EP 398024 A 19901122 (199047) <--
R: AT BE CH DE ES FR GB GR IT LI LU NL SE
JP 03034999 A 19910214 (199113) <--
EP 398024 B1 19930224 (199308) DE 29p A61K049-02 <--

R: AT BE CH DE DK ES FR GB GR IT LI LU NL SE

DE	59000908	G	19930401 (199314)		A61K049-02	<--
US	5308604	A	19940503 (199417)	13p	A61K049-02	<--
ES	2054137	T3	19940801 (199432)		A61K049-02	<--
JP	08019156	B2	19960228 (199613)	13p	C07K014-00	<--

ADT DE 3912792 A **DE 1989-3912792 19890419**; EP 398024 A **EP 1990-107187 19900314**; JP 03034999 A **JP 1990-100546 19900418** ; EP 398024 B1 **EP 1990-107187 19900314**; DE 59000908 G **DE 1990-500908 19900314, EP 1990-107187 19900314**; US 5308604 A **Cont of US 1990-509810 19900417, Cont of US 1991-734123 19910725, US 1992-859273 19920326**; ES 2054137 T3 **EP 1990-107187 19900314**; JP 08019156 B2 **JP 1990-100546 19900418**

FDT DE 59000908 G Based on EP 398024; ES 2054137 T3 Based on EP 398024; JP 08019156 B2 Based on JP 03034999

PRAI **DE 1989-3912792 19890419**

REP 2.Jnl.Ref; US 4466951

IC ICM A61K049-02; C07K014-00
ICS **A61K031-04**; A61K031-045; A61K037-02; A61K038-00; A61K043-00; **A61K047-48**; A61K049-00; C07K001-06; C07K015-06; C07K016-00; G01N033-574; G01N033-68

AB DE 3912792 A UPAB: 19930928
A new conjugate (I) comprises at least: (a) a polyalcohol or derivative (b) an active agent; (c) a linker; and (d) a protein. The components are covalently bound to one another and the polyalcohol has the formula (I) where R1 is CH2OHCHO or CH2NH2, and n is greater than or equal to 1.

USE/ADVANTAGE - (I) is useful for locating tumours and therefore has a therapeutic applicationm as a marker.

1/2

FS CPI EPI

FA AB

MC CPI: B04-B04C5; B04-B04C6; B04-B04D2; B11-C07; B11-C08; B12-K04A1; K09-B; K09-E
EPI: S03-E09E; S03-E14H9

ABEQ EP 398024 B UPAB: 19930928
A conjugate composed of a) at least one polyalcohol or one derivatised polyalcohol, b) at least one active agent, c) at least one linker, and d) a protein, wherein the polyalcohol(s) or the derivatised polyalcohol(s) are polyalcohols or derivatised polyalcohols which are not recognised by the defense system of an organism as exogenous, and the protein is a protein which can be taken up by the tumour specifically or non-specifically and is not recognised by the defense system or an organism as exogenous, characterised in that the polyalcohol(s) or the derivatised polyalcohol(s) are a compound of formula (I) in which R1 is CH2OH,CHO or CH2NH2 and n is 1-10 and in which a gp. (a) can be replaced by CO and wherein zero, one or more OH groups can be replaced by NH2, 19F, C19F3, mono-- or poly-19F-substituted 1-4C alkyl or mono-, dr-, tri-, tetra- or penta-19F-substituted phenyl, or the polyalcohol is glucose, fructose, maltose, sucrose or sorbitol, or the polyalcohol derivative is glucose, fructose, maltose, sucrose or sorbitol, with at least one OH group in these compounds being replaced ;by 19F, C19F3, mono- or poly-19F-substituted 1-4C alkyl or mono, di-, tri-, tetra- or penta-19F-substituted phenyl.

0/2

ABEQ US 5308604 A UPAB: 19940613
Conjugate comprises (i) a (derivatised) poly:alcohol (sorbitol), which is not recognised by the defence system of an organisms as exogenous having at least one OH gp. replaced by X, CX3, mono or poly-X-substd. 1-4C alkyl, mono-, di-, tri-, tetra- or penta-X substd. phenyl (X is 19-isotope of fluorine), (ii) an active agent, (iii) a cyanuric chloride linker, and (iv) analogous scrum albumin. The compounds are connected together in the order (i)-(ii)-(iii)-(iv).

Also claimed are agents for diagnosing and therapy of tumours contg. the claimed conjugate.

USE - Conjugate offers new methods of tumour diagnosis in X-ray diagnosis, computerised tomography, nuclear spin tomography, electron spin resonance spectroscopy or electron microscopy.
Dwg.0/2

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=> fil dpci
FILE 'DPCI' ENTERED AT 16:23:45 ON 04 MAR 2003
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FILE LAST UPDATED: 3 MAR 2003       <20030303/UP>
PATENTS CITATION INDEX, COVERS 1973 TO DATE

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L78  ANSWER 1 OF 2  DPCI  (C) 2003 THOMSON DERWENT
AN   2000-224559 [19]   DPCI
CR   1999-229135 [19]; 1999-254253 [21]; 2000-224558 [19]
DNC  C2000-068643
TI   Bioreductive drug conjugates, useful for treating various conditions
     according to the medicament e.g. anti-infectives or for treating
     conditions associated with hypoxia and/or ischemia.
DC   B03 B05
IN   FREEMAN, S; JAFFER, M; STRATFORD, I
PA   (THER-N) THERAMARK LTD; (UYMA-N) UNIV VICTORIA MANCHESTER
CYC  89
PI   WO 2000010611 A2 20000302 (200019)* EN   45p    A61K047-48
        RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL
            OA PT SD SE SL SZ UG ZW
         W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES
            FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS
            LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ
            TM TR TT UA UG US UZ VN YU ZA ZW
     AU 9954308    A  20000314 (200031)              A61K047-48
     EP 1104408    A2 20010606 (200133)  EN          C07D233-91
         R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
            RO SE SI
     JP 2002523382 W  20020730 (200264)       44p    A61K047-48
ADT  WO 2000010611 A2 WO 1999-GB2620 19990819; AU 9954308 A AU
     1999-54308 19990819; EP 1104408 A2 EP 1999-940311 19990819, WO
     1999-GB2620 19990819; JP 2002523382 W WO 1999-GB2620 19990819
     , JP 2000-565931 19990819
FDT  AU 9954308 A Based on WO 200010611; EP 1104408 A2 Based on WO 200010611;
     JP 2002523382 W Based on WO 200010611
PRAI GB 1998-18156    19980820; GB 1998-18030    19980819
IC   ICM  A61K047-48; C07D233-91
     ICS  A61K031-04; A61K031-415; A61K045-00; A61P001-02; A61P001-04;
          A61P001-16; A61P003-10; A61P009-10; A61P009-12; A61P013-12;
          A61P017-06; A61P025-28; A61P029-00; A61P031-04; A61P035-00;
          A61P037-00; C07C205-06; C07D233-92; C07D233-94; C07D233-95
FS   CPI

CTCS CITATION COUNTERS
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PNC.DI    0              Cited Patents Count (by inventor)
PNC.DX    0              Cited Patents Count (by examiner)
IAC.DI    0              Cited Issuing Authority Count (by inventor)
IAC.DX    0              Cited Issuing Authority Count (by examiner)

PNC.GI    0              Citing Patents Count (by inventor)
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PNC.GX 0 Citing Patents Count (by examiner)
IAC.GI 0 Citing Issuing Authority Count (by inventor)
IAC.GX 0 Citing Issuing Authority Count (by examiner)

CRC.I 0 Cited Literature References Count (by inventor)
CRC.X 4 Cited Literature References Count (by examiner)

CDP CITED PATENTS UPD: 20010227

Cited by Examiner

CITING PATENT	CAT	CITED PATENT	ACCNO
WO 200010611	A	No Citations	

REN LITERATURE CITATIONS UPR: 20010227

Citations by Examiner

CITING PATENT	CAT	CITED LITERATURE
WO 200010611	A	HAY MP ET AL: "Nitroimidazole-based "extruded mustards"designed as reductively activated hypoxia-selective cytotoxins" ANTI-CANCER DRUG DESIGN, vol. 11, no. 5, July 1996 (1996-07), pages 383-402, XP000909800
WO 200010611	A	RAUTH A M ET AL: "Bioreductive therapies: An overview of drugs and their mechanisms of action" INTERNATIONAL JOURNAL OF RADIATION: ONCOLOGY BIOLOGY PHYSICS,US,PERGAMON PRESS, vol. 42, no. 4, 1 November 1998 (1998-11-01), pages 755-762, XP002131257 ISSN: 0360-3016
WO 200010611	A	NUDELMAN A ET AL: "Hypoxic radiosensitizers: substituted styryl derivatives" ARCH. PHARM., vol. 327, no. 10, 1994, pages 619-625, XP000909791
WO 200010611	A	JAFFAR M ET AL: "Bioreductive drugs: Selectivity towards hypoxic tissue" EXPERT OPINION ON THERAPEUTIC PATENTS,GB,ASHLEY PUBLICATIONS, vol. 9, no. 10, 1999, pages 1371-1380, XP002131797 ISSN: 1354-3776

L78 ANSWER 2 OF 2 DPCI (C) 2003 THOMSON DERWENT
AN 2000-224558 [19] DPCI
CR 1999-229135 [19]; 1999-254253 [21]; 2000-224559 [19]
DNC C2000-068642
TI Bioreductive conjugate useful for treating, e.g. fibrotic disorders, ulcerative colitis, psoriasis and peptic ulcers.
DC B05
IN ADAMS, G; BLAKE, D; NAUGHTON, D; STRATFORD, I
PA (ADAM-I) ADAMS M; (THER-N) THERAMARK LTD
CYC 88
PI WO 2000010610 A2 20000302 (200019)* EN 46p A61K047-48
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW
AU 9954296 A 20000314 (200031) A61K047-48

ADT WO 2000010610 A2 WO 1999-GB2606 19990819; AU 9954296 A AU 1999-54296 19990819
FDT AU 9954296 A Based on WO 200010610
PRAI **GB 1998-18156 19980820**; GB 1998-18027 19980819
IC ICM A61K047-48
FS CPI

CTCS CITATION COUNTERS

PNC.DI	0	Cited Patents Count (by inventor)
PNC.DX	1	Cited Patents Count (by examiner)
IAC.DI	0	Cited Issuing Authority Count (by inventor)
IAC.DX	1	Cited Issuing Authority Count (by examiner)
PNC.GI	0	Citing Patents Count (by inventor)
PNC.GX	0	Citing Patents Count (by examiner)
IAC.GI	0	Citing Issuing Authority Count (by inventor)
IAC.GX	0	Citing Issuing Authority Count (by examiner)
CRC.I	0	Cited Literature References Count (by inventor)
CRC.X	10	Cited Literature References Count (by examiner)

CDP CITED PATENTS UPD: 20010227

Cited by Examiner

CITING PATENT	CAT	CITED PATENT	ACCNO
WO 200010610	A	WO 9835701 A	1998-506286/43
	PA:	(THER-N) THERAMARK LTD	
	IN:	ADAMS, G; BLAKE, D; JAFFAR, M; MORRIS, C; NAUGHTON, D; NAYLOR, M; STRATFORD, I	

REN LITERATURE CITATIONS UPR: 20010227

Citations by Examiner

CITING PATENT	CAT	CITED LITERATURE
WO 200010610	A	RAUTH A.M. ET AL: "Bioreductive therapies: An overview of drugs and their mechanisms of action." INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY BIOLOGY PHYSICS, (1998) 42/4 (755-762). , XP002131257
WO 200010610	A	BEALL, HOWARD D. ET AL: "Indolequinone Antitumor Agents: Correlation between Quinone Structure, Rate of Metabolism by Recombinant Human NAD(P)H:Quinone Oxidoreductase, and in Vitro Cytotoxicity" J. MED. CHEM. (1998), 41(24), 4755-4766 , XP002131258
WO 200010610	A	NAYLOR M.A. ET AL: "Indolequinone antitumor agents: Reductive activation and elimination from (5-methoxy-1-methyl-4,7-dioxoindol-3-yl)me thyl derivatives and hypoxia - selective cytotoxicity in vitro." JOURNAL OF MEDICINAL CHEMISTRY, (1998) 41/15 (2720-2731). , XP002131259
WO 200010610	A	NAYLOR, MATTHEW A. ET AL: "2-Cyclopropylindoloquinones and Their Analogs As Bioreductively Activated Antitumor Agents:

		Structure-Activity in Vitro and Efficacy in Vivo" J. MED. CHEM. (1997), 40(15), 2335-2346 , XP002131260
WO 200010610	A	EVERETT S A ET AL: "Bioreductively-activated prodrugs for targeting hypoxic tissues: elimination of aspirin from 2-nitroimidazole derivatives" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS,GB,OXFORD, vol. 9, no. 9, 3 May 1999 (1999-05-03), pages 1267-1272, XP004163956 ISSN: 0960-894X
WO 200010610	A	PARVEEN I ET AL: "2-nitroimidazol-5-ylmethyl as a potential bioreductively activated prodrug system: reductively triggered release of the PARP inhibitor 5-bromoisoquinolinone" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS,GB,OXFORD, vol. 9, no. 14, 19 July 1999 (1999-07-19), pages 2031-2036, XP004171631 ISSN: 0960-894X
WO 200010610	A	JAFFAR M ET AL: "Prodrugs for targeting hypoxic tissues: regiospecific elimination of aspirin from reduced indolequinones" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS,GB,OXFORD, vol. 9, no. 1, January 1999 (1999-01), pages 113-118, XP004154788 ISSN: 0960-894X
WO 200010610	A	CHIKHALE P ET AL: "TUMOR TARGETED PRODRUGS: REDOX-ACTIVATION OF CONFORMATIONALLY CONSTRAINED, BIOREDUCTIVE MELPHALAN PRODRUGS" PROCEEDINGS OF THE ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH,US,PHILADELPHIA, AACR, vol. 38, 1997, page 432 XP002052354
WO 200010610	A	BERGLUND R A: "BIOREDUCTIVE HETEROSUBSTITUTED QUINONE ANTITUMOR DRUG DELIVERY AGENTS" DISSABS, XP002052358
WO 200010610	A	JAFFAR M. ET AL: "Bioreductive drugs: Selectivity towards hypoxic tissue." EXPERT OPINION ON THERAPEUTIC PATENTS, (1999) 9/10 (1371-1380). , XP002131797

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FILE COVERS 1907 - 4 Mar 2003 VOL 138 ISS 10
FILE LAST UPDATED: 3 Mar 2003 (20030303/ED)

This file contains CAS Registry Numbers for easy and accurate
substance identification.

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L20 ANSWER 1 OF 5 HCAPLUS COPYRIGHT 2003 ACS
AN 2000:144773 HCAPLUS
DN 132:185464
TI **Bioreductive** conjugate for drug targeting
IN **Freeman, Sally; Jaffer, Mohammed; Stratford, Ian**
PA Theramark Limited, UK
SO PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM **A61K047-48**
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	WO 2000010611	A2	20000302	WO 1999-GB2620	19990819	<--
	WO 2000010611	A3	20000824			
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	RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
	CA 2342162	AA	20000302	CA 1999-2342162	19990819	<--
	AU 9954308	A1	20000314	AU 1999-54308	19990819	<--
	EP 1104408	A2	20010606	EP 1999-940311	19990819	<--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
	JP 2002523382	T2	20020730	JP 2000-565931	19990819	<--
PRAI	GB 1998-18030	A	19980819	<--		
	GB 1998-18156	A	19980820	<--		
	WO 1999-GB2620	W	19990819	<--		

OS MARPAT 132:185464
AB A **bioreductive** conjugate comprises a **bioreductive** moiety with at least one therapeutic agent linked thereto and physiol. acceptable derivs. thereof. The **bioreductive** moiety incorporates an arom. ring substituted with a **nitro** group and the conjugate is such that **bioredn.** of the **nitro** group causes release of the therapeutic agent by a through bond elimination and the residue of the **bioreductive** moiety to undergo an intramol. **cyclization** reaction in which the **nitrogen** of the original **nitro** group provides an atom of the thus formed ring (no data).
ST **bioreductive** conjugate drug targeting
IT Intestine, disease
(Crohn's; **bioreductive** conjugate for drug targeting)
IT AIDS (disease)
Alzheimer's disease
Analgesics
Anesthetics
Anti-infective agents
Anti-inflammatory agents
Antibiotics
Antitumor agents
Antiviral agents
Atherosclerosis
Cyclization

Cystic fibrosis
Diabetes mellitus
Drug targeting
Drugs
Epilepsy
Fibrosis
Hypertension
Hypoxia, animal
Inflammation
Ischemia
Kidney, disease
Liver, disease
Neoplasm
Osteoarthritis
Psoriasis
Sepsis
Wound healing
(**bioreductive** conjugate for drug targeting)

IT Mental disorder
(dementia; **bioreductive** conjugate for drug targeting)

IT Ulcer
(diabetic; **bioreductive** conjugate for drug targeting)

IT Digestive tract
Nervous system
(disease; **bioreductive** conjugate for drug targeting)

IT Intestine, disease
(duodenum, ulcer; **bioreductive** conjugate for drug targeting)

IT Injury
(from cardiovascular reperfusion; **bioreductive** conjugate for drug targeting)

IT Intestine, disease
(inflammatory; **bioreductive** conjugate for drug targeting)

IT Ulcer
(peptic; **bioreductive** conjugate for drug targeting)

IT Periodontium
(periodontitis, chronic; **bioreductive** conjugate for drug targeting)

IT Alkylation
(self-; **bioreductive** conjugate for drug targeting)

IT Animal tissue
(soft; **bioreductive** conjugate for drug targeting)

IT Brain, disease
(stroke; **bioreductive** conjugate for drug targeting)

IT Stomach, disease
(ulcer; **bioreductive** conjugate for drug targeting)

IT Intestine, disease
(ulcerative colitis; **bioreductive** conjugate for drug targeting)

L20 ANSWER 2 OF 5 HCAPLUS COPYRIGHT 2003 ACS
AN 2000:144772 HCAPLUS
DN 132:189689
TI **Bioreductive** conjugates for drug targeting
IN Adams, Ged; Blake, David; Naughton, Declan; **Stratford, Ian**
PA Theramark Limited, UK; Adams, Margaret
SO PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM **A61K047-48**
CC 1-12 (Pharmacology)
FAN.CNT 4

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

PI	WO 2000010610	A2	20000302	WO 1999-GB2606	19990819 <--
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9954296	A1	20000314	AU 1999-54296	19990819 <--
PRAI	GB 1998-18027	A	19980819		
	GB 1998-18156	A	19980820 <--		
	WO 1999-GB2606	W	19990819		

OS MARPAT 132:189689

AB The use of a **bioreductive** conjugate comprised of a noncytotoxic **bioreductive** moiety having linked thereto at least one therapeutic agent, and salts thereof, is disclosed for the healing of wounds and the treatment of fibrotic disorders, ulcerative colitis, inflammatory bowel disease, epilepsy, cardiovascular reperfusion injury, cerebral reperfusion injury, hypertension, cystic fibrosis, psoriasis, para-psoriasis, peptic ulcers, gastric ulcers, duodenal ulcers, diabetic ulcers dementia, oncol., AIDS, rheumatoid arthritis, diabetes, and ischemia. Various specific conjugates for treating these conditions are also disclosed.

ST **bioreductive** conjugate drug targeting therapeutic

IT Transforming growth factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(TGF.beta.3; **bioreductive** conjugates for drug targeting)

IT DNA
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(alkylation; **bioreductive** conjugates for drug targeting)

IT Psoriasis
(and para-psoriasis; **bioreductive** conjugates for drug targeting)

IT Mitosis
(antimitotics; **bioreductive** conjugates for drug targeting)

IT Actins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(assembly and organization modulators; **bioreductive** conjugates for drug targeting)

IT Alkylation
(biochem.; **bioreductive** conjugates for drug targeting)

IT Anti-AIDS agents
Anti-inflammatory agents
Anti-ischemic agents
Anticoagulants
Anticonvulsants
Antidiabetic agents
Antihypertensives
Antirheumatic agents
Antitumor agents
Antiulcer agents
Apoptosis
Cardiovascular agents
Cystic fibrosis
Drug metabolism
Drug targeting
Fibrinolytics
Fibrosis
Hypoxia, animal
Immunomodulators

Immunosuppressants
Platelet aggregation inhibitors
Radical scavengers
Vasodilators
Wound healing promoters
(**bioreductive** conjugates for drug targeting)

IT Interleukin 10
Interleukin 4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**bioreductive** conjugates for drug targeting)

IT Interleukin 1
Platelet-derived growth factors
Sex hormones
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**bioreductive** conjugates for drug targeting)

IT Ion channel blockers
(calcium; **bioreductive** conjugates for drug targeting)

IT Drugs
(conjugates; **bioreductive** conjugates for drug targeting)

IT Corticosteroids, biological studies
Steroids, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(conjugates; **bioreductive** conjugates for drug targeting)

IT Diabetes mellitus
(diabetic ulcer; **bioreductive** conjugates for drug targeting)

IT Cell cycle
(drugs specific for; **bioreductive** conjugates for drug targeting)

IT Intestine, disease
(duodenum, ulcer; **bioreductive** conjugates for drug targeting)

IT Growth factors, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(growth factor neutralizing agents; **bioreductive** conjugates for drug targeting)

IT Intestine, disease
(inflammatory; **bioreductive** conjugates for drug targeting)

IT Lung, neoplasm
Lung, neoplasm
(inhibitors, A549; **bioreductive** conjugates for drug targeting)

IT Interleukin 6
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; **bioreductive** conjugates for drug targeting)

IT Reperfusion
(injury, including cerebral reperfusion injury; **bioreductive** conjugates for drug targeting)

IT Integrins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(integrin receptor activation inhibitors; **bioreductive** conjugates for drug targeting)

IT Antitumor agents
Antitumor agents
(lung, A549; **bioreductive** conjugates for drug targeting)

IT Ulcer
(peptic; **bioreductive** conjugates for drug targeting)

IT Stomach, disease
(ulcer; **bioreductive** conjugates for drug targeting)

IT Intestine, disease
(ulcerative colitis; **bioreductive** conjugates for drug

targeting)

IT Proteins, general, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(wound site, growth factor-assocd.; **bioreductive** conjugates for drug targeting)

IT Adrenoceptor antagonists
(.beta.-; **bioreductive** conjugates for drug targeting)

IT Polysaccharides, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.beta.-glycans, sol.; **bioreductive** conjugates for drug targeting)

IT Transforming growth factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(.beta.1-; **bioreductive** conjugates for drug targeting)

IT Transforming growth factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(.beta.2-; **bioreductive** conjugates for drug targeting)

IT Interferons
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(.gamma.; **bioreductive** conjugates for drug targeting)

IT 114560-25-7 114560-34-8, EO 8 161518-24-7, RB 94547J
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**bioreductive** conjugates for drug targeting)

IT 50-06-6D, Phenobarbitone, conjugates, biological studies 50-24-8D, Prednisolone, conjugates 50-78-2D, Aspirin, conjugates 52-53-9D, Verapamil, conjugates 52-67-5D, Penicillamine, conjugates 53-86-1D, Indomethacin, conjugates 57-41-0D, Phenytoin, conjugates 58-32-2D, Dipyridamole, conjugates 59-05-2D, Methotrexate, conjugates 66-97-7D, Psoralen, conjugates 89-57-6D, Mesalazine, conjugates 89-57-6D, 5-Aminosalicylic acid, derivs., conjugates 118-42-3D, Hydroxychloroquine, conjugates 305-03-3D, Chlorambucil, conjugates 443-48-1D, Metronidazole, conjugates 446-86-6D, Azathioprine, conjugates 599-79-1D, Sulfasalazine, conjugates 1069-66-5D, Sodium valproate, conjugates 1406-16-2D, Vitamin D, analogs, conjugates 6556-11-2D, Inositol nicotinate, conjugates 12244-57-4D, Myochrysine, conjugates 15307-86-5D, Diclofenac, conjugates 15687-27-1D, Ibuprofen, conjugates 21829-25-4D, Niphedipine, conjugates 22204-53-1D, Naproxen, conjugates 26171-23-3D, Tolmetin, conjugates 29679-58-1D, Fenoprofen, conjugates 38194-50-2D, Sulindac, conjugates 51234-28-7D, Benoxaprofen, conjugates 56180-94-0D, Acarbose, conjugates 59865-13-3D, Cyclosporin A, conjugates 62571-86-2D, Captopril, conjugates 67763-97-7D, Insulin-like growth factor II, conjugates 73590-58-6D, Omeprazole, conjugates 79217-60-0D, Cyclosporin, derivs., conjugates 87333-19-5D, Ramipril, conjugates 87679-37-6D, Trandolapril, conjugates 97240-79-4D, Topiramate, conjugates 103577-45-3D, Lansoprazole, conjugates 113194-81-3, TMK 209 117976-89-3D, Rabeprazole, conjugates 259876-40-9, TMK 210 259876-41-0, TMK 207
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**bioreductive** conjugates for drug targeting)

IT 106096-92-8, Acidic fibroblast growth factor 106096-93-9, Basic fibroblast growth factor
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**bioreductive** conjugates for drug targeting)

IT 9015-82-1, Angiotensin-converting enzyme 9025-82-5, Phosphodiesterase 9036-21-9, Phosphodiesterase IV 9055-65-6, Prostaglandin synthetase 9068-52-4, Phosphodiesterase V 81669-70-7, Metalloprotease 99676-46-7, Kexin 125978-95-2, Nitric oxide synthase

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; **bioreductive** conjugates for drug targeting)
IT 57285-09-3, Inhibin 114949-22-3, Activin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(stimulators; **bioreductive** conjugates for drug targeting)

L20 ANSWER 3 OF 5 HCAPLUS COPYRIGHT 2003 ACS
AN 1999:577033 HCAPLUS
DN 131:194269
TI Prodrug activating agent comprising localization domain-prodrug activation domain fusions and hematopoietic cells producing them for use as pharmaceuticals
IN **Stratford, Ian James**; Patterson, Adam Vorn; Kingsman, Susan Mary; Kan, On; Griffiths, Leigh; Mitrophanous, Kyriacos
PA Oxford Biomedica (Uk) Ltd., UK
SO PCT Int. Appl., 190 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C12N015-62
ICS C12N005-10; C12N015-86; C12N009-02; **A61K047-48**; A61K038-44; C12N007-01
CC 1-1 (Pharmacology)
Section cross-reference(s): 3
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9945127	A2	19990910	WO 1999-GB674	19990305
	WO 9945127	A3	20000224		
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	CA 2322664	AA	19990910	CA 1999-2322664	19990305
	AU 9932670	A1	19990920	AU 1999-32670	19990305
	EP 1068338	A2	20010117	EP 1999-937944	19990305
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRAI	GB 1998-4841	A	19980306
	GB 1998-18103	A	19980819
	GB 1999-2081	A	19990129
	WO 1999-GB674	W	19990305

AB A prodrug activating agent comprising: (a) a localization domain and (b) a prodrug activation domain for activating a prodrug in a target cell, nucleic acids and vectors encoding these agents, hematopoietic stem cells expressing the nucleic acid, and pharmaceutical compns. contg. said agents or nucleic acids are disclosed. Chimeric genes for numerous prodrug activating agents were prepd. One such gene encoded a fusion of SV40 large T antigen nuclear localization signal fused to a human cytochrome P 450 **reductase** fragment comprising the FAD- and NADH-binding domains. Equine infectious anemia virus vectors for expression of such chimeric genes were also prepd. When macrophages infected with adenovirus contg. a CMV promoter fused to human cytochrome P 450-2B6 cDNA were incubated with tumor cells in the presence of cyclophosphamide, the tumor cells were killed. Under the same conditions, tumor cells in the presence of unmodified macrophages and cyclophosphamide were not killed.
ST macrophage cytochrome P450 expressing cyclophsphamide antitumor agent; prodrug activating agent localization domain cytochrome P450

reductase

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(CYP2B6; prodrug activating agent comprising localization domain-prodrug activation domain fusions and hematopoietic cells producing them for use as pharmaceuticals)

IT Antiarteriosclerotics
(antiatherosclerotics, use with; prodrug activating agent comprising localization domain-prodrug activation domain fusions and hematopoietic cells producing them for use as pharmaceuticals)

IT Macrophage
(expression of chimeric protein in; prodrug activating agent comprising localization domain-prodrug activation domain fusions and hematopoietic cells producing them for use as pharmaceuticals)

IT Peptides, biological studies
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(nuclear localization signal; prodrug activating agent comprising localization domain-prodrug activation domain fusions and hematopoietic cells producing them for use as pharmaceuticals)

IT Pharmacokinetics
(of indoloquinone acetal salicylic acid conjugate; prodrug activating agent comprising localization domain-prodrug activation domain fusions and hematopoietic cells producing them for use as pharmaceuticals)

IT Adeno-associated virus
Antirheumatic agents
Genetic engineering
(prodrug activating agent comprising localization domain-prodrug activation domain fusions and hematopoietic cells producing them for use as pharmaceuticals)

IT Fusion proteins (chimeric proteins)
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prodrug activating agent comprising localization domain-prodrug activation domain fusions and hematopoietic cells producing them for use as pharmaceuticals)

IT Chimeric gene
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(prodrug activating agent comprising localization domain-prodrug activation domain fusions and hematopoietic cells producing them for use as pharmaceuticals)

IT Enzymes, biological studies
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prodrug-activating; prodrug activating agent comprising localization domain-prodrug activation domain fusions and hematopoietic cells producing them for use as pharmaceuticals)

IT Drug delivery systems
(prodrugs; prodrug activating agent comprising localization domain-prodrug activation domain fusions and hematopoietic cells producing them for use as pharmaceuticals)

IT Adenoviridae
Lentivirus
Poxviridae
Retroviral vectors
Virus vectors
(role in delivery and expression of chimeric protein; prodrug activating agent comprising localization domain-prodrug activation domain fusions and hematopoietic cells producing them for use as pharmaceuticals)

IT Hematopoietic precursor cell
(stem; prodrug activating agent comprising localization domain-prodrug activation domain fusions and hematopoietic cells producing them for use as pharmaceuticals)
IT Muscular dystrophy
(use in treatment of; prodrug activating agent comprising localization domain-prodrug activation domain fusions and hematopoietic cells producing them for use as pharmaceuticals)
IT Anti-inflammatory agents
Antitumor agents
(use with; prodrug activating agent comprising localization domain-prodrug activation domain fusions and hematopoietic cells producing them for use as pharmaceuticals)
IT Equine infectious anemia virus
(vectors; prodrug activating agent comprising localization domain-prodrug activation domain fusions and hematopoietic cells producing them for use as pharmaceuticals)
IT 241805-93-6P 241806-02-0P 241806-03-1P 241806-04-2P 241806-05-3P
241806-06-4P 241806-07-5P 241806-08-6P 241806-09-7P 241806-10-0P
RL: BPN (Biosynthetic preparation); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(amino acid sequence; prodrug activating agent comprising localization domain-prodrug activation domain fusions and hematopoietic cells producing them for use as pharmaceuticals)
IT 9035-51-2P, Cytochrome P 450, biological studies 9039-06-9P, Cytochrome P 450 **reductase**
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prodrug activating agent comprising localization domain-prodrug activation domain fusions and hematopoietic cells producing them for use as pharmaceuticals)
IT 241150-59-4P
RL: BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(prodrug activating agent comprising localization domain-prodrug activation domain fusions and hematopoietic cells producing them for use as pharmaceuticals)
IT 50-07-7, Mitomycin C 50-18-0, Cyclophosphamide 27314-97-2, Tirapazamine
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(prodrug activating agent comprising localization domain-prodrug activation domain fusions and hematopoietic cells producing them for use as pharmaceuticals)
IT 210578-33-9
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(prodrug activating agent comprising localization domain-prodrug activation domain fusions and hematopoietic cells producing them for use as pharmaceuticals)
IT 50-78-2, Acetylsalicylic acid
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); THU (Therapeutic use); BIOL (Biological study); FORM (Formation, nonpreparative); USES (Uses)
(prodrug activating agent comprising localization domain-prodrug activation domain fusions and hematopoietic cells producing them for use as pharmaceuticals)
IT 5538-51-2, Acetylsalicyloyl chloride 161518-24-7, 3-Hydroxymethyl-5-methoxy-1,2-dimethylindole-4,7-dione
RL: RCT (Reactant); RACT (Reactant or reagent)
(prodrug activating agent comprising localization domain-prodrug activation domain fusions and hematopoietic cells producing them for

use as pharmaceuticals)

L20 ANSWER 4 OF 5 HCAPLUS COPYRIGHT 2003 ACS
AN 1999:577032 HCAPLUS
DN 131:195451
TI Enhanced prodrug activation via a chimeric protein with a cytochrome P450 or cytochrome P450 **reductase** activation domain
IN **Stratford, Ian James**; Patterson, Adam Vorn; Kingsman, Susan Mary; Kan, On; Griffiths, Leigh; Mitrophanous, Kyriacos
PA Oxford Biomedica (Uk) Ltd., UK
SO PCT Int. Appl., 150 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C12N015-62
ICS C12N005-10; C12N015-86; C12N009-02; **A61K047-48**; A61K038-44; C12N007-01
CC 3-2 (Biochemical Genetics)
Section cross-reference(s): 1, 7
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9945126	A2	19990910	WO 1999-GB672	19990305
	WO 9945126	A3	20000210		
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9932668	A1	19990920	AU 1999-32668	19990305
	JP 2002505341	T2	20020219	JP 2000-534657	19990305
PRAI	GB 1998-4841	A	19980306		
	GB 1998-18103	A	19980819		
	GB 1999-2081	A	19990129		
	WO 1999-GB672	W	19990305		

AB In order to maximize the potential of enzyme prodrug therapy, it is important to use a delivery system and an enzyme/drug combination that shows effective target cell-specific killing. Preferably, the no. of target cells destroyed is increased by creating a large bystander effect that displays minimal systemic toxicity. The present invention aims to address these needs by providing a prodrug activating agent comprising: a) a localization domain and b) a prodrug activation domain for activating a prodrug in a target cell. Preferably, the prodrug activating agent is a chimeric protein wherein the prodrug activating domain is cytochrome P 450 or cytochrome P 450 **reductase**. In one embodiment, the chimeric gene encoding the prodrug activating agent is contained within a viral vector and is expressed in a modified hematopoietic stem cell (MHSC). The invention can be used in the treatment of a variety of diseases, including cancer, inflammation, atherosclerosis, and muscular dystrophy.
ST chimeric protein cytochrome P450 **reductase** prodrug activation
IT Antiarteriosclerotics
(antiatherosclerotics, use with; enhanced prodrug activation via a chimeric protein with a cytochrome P 450 or cytochrome P 450 **reductase** activation domain)
IT Fusion proteins (chimeric proteins)
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(comprising a localization domain and an activation domain; enhanced prodrug activation via a chimeric protein with a cytochrome P 450 or

cytochrome P 450 **reductase** activation domain)

IT Promoter (genetic element)
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(cytomegalovirus, use in expression of chimeric protein; enhanced prodrug activation via a chimeric protein with a cytochrome P 450 or cytochrome P 450 **reductase** activation domain)

IT Chimeric gene
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(encoding a protein having a localization domain and an activation domain; enhanced prodrug activation via a chimeric protein with a cytochrome P 450 or cytochrome P 450 **reductase** activation domain)

IT Genetic engineering
(enhanced prodrug activation via a chimeric protein with a cytochrome P 450 or cytochrome P 450 **reductase** activation domain)

IT Macrophage
(expression of chimeric protein in; enhanced prodrug activation via a chimeric protein with a cytochrome P 450 or cytochrome P 450 **reductase** activation domain)

IT Drug delivery systems
(prodrugs; enhanced prodrug activation via a chimeric protein with a cytochrome P 450 or cytochrome P 450 **reductase** activation domain)

IT Adeno-associated virus
Adenoviridae
Lentivirus
Poxviridae
Retroviral vectors
Virus vectors
(role in delivery and expression of chimeric protein; enhanced prodrug activation via a chimeric protein with a cytochrome P 450 or cytochrome P 450 **reductase** activation domain)

IT Hematopoietic precursor cell
(stem, expression of chimeric protein in; enhanced prodrug activation via a chimeric protein with a cytochrome P 450 or cytochrome P 450 **reductase** activation domain)

IT Muscular dystrophy
(use in treatment of; enhanced prodrug activation via a chimeric protein with a cytochrome P 450 or cytochrome P 450 **reductase** activation domain)

IT Anti-inflammatory agents
Antitumor agents
(use with; enhanced prodrug activation via a chimeric protein with a cytochrome P 450 or cytochrome P 450 **reductase** activation domain)

IT 9035-51-2, Cytochrome P 450, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(2B6; enhanced prodrug activation via a chimeric protein with a cytochrome P 450 or cytochrome P 450 **reductase** activation domain)

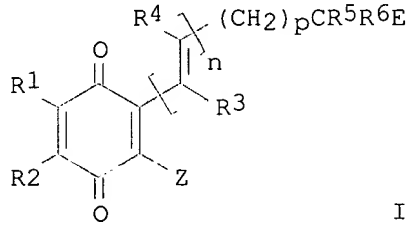
IT 9039-06-9, Cytochrome P 450 **reductase**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(enhanced prodrug activation via a chimeric protein with a cytochrome P 450 or cytochrome P 450 **reductase** activation domain)

L20 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2003 ACS
AN 1998:568742 HCAPLUS
DN 129:202857
TI Drug targeting with **bioreductive** conjugates to areas of hypoxic or ischemic tissue
IN Blake, David; Naughton, Declan; Adams, Ged; **Stratford, Ian;**

Morris, Christopher; Jaffar, Mohammed; Naylor, Matthew
PA Theramark Limited, UK
SO PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM **A61K047-48**
CC 27-10 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1, 32, 63
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9835701	A1	19980820	WO 1998-GB461	19980213
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9862228	A1	19980908	AU 1998-62228	19980213
	AU 751145	B2	20020808		
	EP 988057	A1	20000329	EP 1998-904282	19980213
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
	JP 2001512425	T2	20010821	JP 1998-533318	19980213
PRAI	GB 1997-3002	A	19970213		
	GB 1997-12090	A	19970610		
	WO 1998-GB461	W	19980213		

OS MARPAT 129:202857
GI



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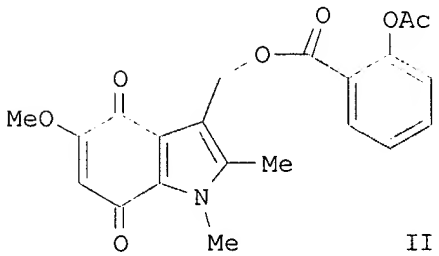

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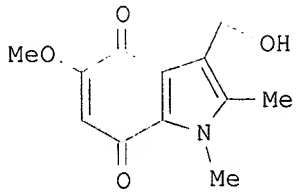

III

AB Novel **bioreductive** conjugates, A(B)n, comprising a non-cytotoxic **bioreductive** moiety (A) linked-thereto at least one therapeutic agent (B, n = 1 - 3) and I [R1, R2 = H, halogen, alkyl, OH, alkoxy, SH, alkylthio, NH2, monoalkylamino, dialkylamino, carboxy, alkoxycarbonyl, CONH2, alkylaminocarbonyl; R1R2 = (un)substituted carbocyclic or heterocyclic ring; Z = (un)substituted alkyl, alkenyl, aryl, aralkyl; R3,

R4, R5, R6 = H, alkyl, alkenyl; E = (un)linked therapeutic agent; m = 0 - 3; p = 0, 2; when m = 1 then p = 0], are described. Thus, **bioreductive** conjugate II was prepd. via esterification of 2-AcOC6H4COCl with indoledione III. The pharmacokinetics of II were studied and showed that aspirin had been released from the conjugate.

ST **bioreductive** conjugate drug targeting hypoxia ischemia; acetylsalicyloyl chloride esterification hydroxymethylmethoxyindoledione deriv; aspirin **bioreductive** conjugate prodrug pharmacokinetics

IT Drug delivery systems
Drug targeting
Hypoxia, animal
Ischemia
Rheumatoid arthritis
(drug targeting with **bioreductive** conjugates to areas of hypoxia or ischemia)

IT Drug delivery systems
(prodrugs; drug targeting with **bioreductive** conjugates to areas of hypoxia or ischemia)

IT 50-78-2P, Aspirin
RL: BPN (Biosynthetic preparation); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(drug targeting with **bioreductive** conjugates to areas of hypoxia ischemia)

IT 192820-71-6P
RL: BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(drug targeting with **bioreductive** conjugates to areas of hypoxia ischemia)

IT 5538-51-2, 2-Acetylsalicyloyl chloride 161518-24-7, 3-Hydroxymethyl-5-methoxy-1,2-dimethylindole-4,7-dione
RL: RCT (Reactant); RACT (Reactant or reagent)
(drug targeting with **bioreductive** conjugates to areas of hypoxia ischemia)

RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD

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(10) Sequus Pharm Inc; WO 9625147 A 1996 HCAPLUS

=> d all tot

L93 ANSWER 1 OF 11 HCAPLUS COPYRIGHT 2003 ACS
AN 1999:650852 HCAPLUS
DN 132:37
TI Bioreductive drugs: selectivity towards hypoxic tissue
AU **Jaffar, Mohammed**; Stratford, Ian J.
CS School of Pharmacy and Pharmaceutical Sciences, University of Manchester, Manchester, M13 9PL, UK
SO Expert Opinion on Therapeutic Patents (**1999**), **9**(**10**), **1371**-1380
CODEN: EOTPEG; ISSN: 1354-3776
PB Ashley Publications

DT Journal; General Review
LA English
CC 1-0 (Pharmacology)
Section cross-reference(s): 63
AB A review with 63 refs. Bioreductive prodrugs have been developed to effectively target the hypoxic cell population of tumors. The mechanism of their selective activation in hypoxic tissue is based on the redn. of their oxidative substituents that upon redn. afford the active species. The redn. of the products is brought about by utilizing some of the reductive enzymes that are present in all solid tumors. Investigations into the mode of action of bioreductive drugs have resulted in their use as delivery systems that can effectively release a secondary agent preferentially under hypoxic conditions for the treatment of hypoxic disorders.
ST review bioreductive drug hypoxic tumor selectivity
IT Antitumor agents
Drug targeting
Hypoxia, animal
(bioreductive products that selectivity target hypoxic tumor tissue)
IT Drug delivery systems
(prodrugs; bioreductive products that selectivity target hypoxic tumor tissue)
RE.CNT 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD
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L93 ANSWER 2 OF 11 HCAPLUS COPYRIGHT 2003 ACS
AN 1999:504276 HCAPLUS
DN 131:276879
TI 2-Nitroimidazol-5-ylmethyl as a potential bioreductively activated prodrug system: reductively triggered release of the PARP inhibitor 5-bromoisoquinolinone
AU **Parveen, Ifat**; Naughton, Declan P.; Whish, William J. D.; Threadgill, Michael D.
CS Department of Pharmacy & Pharmacology, University of Bath, Bath, BA2 7AY, UK
SO Bioorganic & Medicinal Chemistry Letters (**1999**), **9**(**14**), **2031**-2036
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier Science Ltd.
DT Journal
LA English
CC 63-5 (Pharmaceuticals)
Section cross-reference(s): 1, 28
AB 5-Chloromethyl-1-methyl-2-nitroimidazole reacted efficiently with the anion derived from 5-bromoisoquinolin-1-one to give 5-bromo-2-((1-methyl-2-nitroimidazol-5-yl)methyl)isoquinolin-1-one. Biomimetic redn. affected release of the 5-bromoisoquinolin-1-one. The 2-nitroimidazol-5-ylmethyl unit thus has potential for development as a general prodrug system for selective drug delivery to hypoxic tissues.
ST nitroimidazolylmethyl isoquinolinone prepn prodrug PARP inhibitor; bromoisoquinolinone release nitroimidazolylmethyl prodrug PARP inhibitor
IT Reduction
(biol.; prepn. of bioreductively activated prodrug of PARP inhibitor 5-bromoisoquinolinone contg. nitroimidazolylmethyl unit)
IT Drug delivery systems
(prodrugs; prepn. of bioreductively activated prodrug of PARP inhibitor 5-bromoisoquinolinone contg. nitroimidazolylmethyl unit)
IT 190777-77-6P
RL: BPR (Biological process); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC (Process); RACT (Reactant or reagent)
(prepn. of bioreductively activated prodrug of PARP inhibitor 5-bromoisoquinolinone contg. nitroimidazolylmethyl unit)

IT 245677-37-6P
RL: BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(prepn. of bioreductively activated prodrug of PARP inhibitor 5-bromoisoquinolinone contg. nitroimidazolylmethyl unit)
IT 9055-67-8, Poly(ADP-ribose) synthetase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(prepn. of bioreductively activated prodrug of PARP inhibitor 5-bromoisoquinolinone contg. nitroimidazolylmethyl unit)
IT 491-30-5, 1(2H)-Isoquinolinone
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(prepn. of bioreductively activated prodrug of PARP inhibitor 5-bromoisoquinolinone contg. nitroimidazolylmethyl unit)
IT 39070-12-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of bioreductively activated prodrug of PARP inhibitor 5-bromoisoquinolinone contg. nitroimidazolylmethyl unit)
IT 39070-13-8P 39070-14-9P 70758-25-7P 77747-69-4P 87544-76-1P 231950-42-8P 245677-36-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of bioreductively activated prodrug of PARP inhibitor 5-bromoisoquinolinone contg. nitroimidazolylmethyl unit)
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L93 ANSWER 3 OF 11 HCAPLUS COPYRIGHT 2003 ACS
AN 1999:310755 HCAPLUS
DN 131:102235
TI Bioreductively-activated prodrugs for targeting hypoxic tissues: elimination of aspirin from 2-nitroimidazole derivatives
AU **Everett, S. A.**; Naylor, M. A.; Patel, K. B.; Stratford, M. R. L.; Wardman, P.
CS Gray Laboratory Cancer Research Trust, Mount Vernon Hospital, Middlesex, HA6 2JR, UK
SO Bioorganic & Medicinal Chemistry Letters (**1999**), **9**(**9**), **1267**-1272
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier Science Ltd.
DT Journal

LA English
CC 28-9 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 22, 63
AB 2-Nitroimidazoles were synthesized substituted with aspirin or salicylic acid, as leaving groups linked through the (imidazol-5-yl)methyl position. Activation of aq. solns. by CO2.cntdot.- (a model one-electron reductant) resulted in release of aspirin or salicylate, probably via the 2-hydroxyaminoimidazole. The analogous 2-nitroimidazole with bromide as leaving group eliminated bromide in <1 ms via the radical-anion.
ST prodrug nitroimidazole aspirin salicylate prepn; mechanism reductive elimination bromide aspirin
IT Drug delivery systems
(prodrugs; prepn. of bioreductively-activated prodrugs for targeting hypoxic tissues and elimination of aspirin from 2-nitroimidazole derivs.)
IT 231950-42-8P 231950-43-9P
RL: PEP (Physical, engineering or chemical process); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); PROC (Process); RACT (Reactant or reagent)
(prepn. of bioreductively-activated prodrugs for targeting hypoxic tissues and elimination of aspirin from 2-nitroimidazole derivs.)
IT 5538-51-2, Acetylsalicyloyl chloride 39070-14-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of bioreductively-activated prodrugs for targeting hypoxic tissues and elimination of aspirin from 2-nitroimidazole derivs.)
IT 50-78-2P, Aspirin 231950-44-0P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of bioreductively-activated prodrugs for targeting hypoxic tissues and elimination of aspirin from 2-nitroimidazole derivs.)
RE.CNT 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD
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L93 ANSWER 4 OF 11 HCAPLUS COPYRIGHT 2003 ACS
AN 1999:52830 HCAPLUS
DN 130:246299
TI Prodrugs for targeting hypoxic tissues: regiospecific elimination of aspirin from reduced indolequinones
AU **Jaffar, M.**; Everett, S. A.; Naylor, M. A.; Moore, S. G.; Ulhaq, S.; Patel, K. B.; Stratford, M. R. L.; Nolan, J.; Wardman, P.; Stratford, I. J.
CS School of Pharmacy, University of Manchester, Manchester, M13 9PL, UK
SO Bioorganic & Medicinal Chemistry Letters (**1999**), **9**(1), **113**-118
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier Science Ltd.
DT Journal
LA English
CC 1-3 (Pharmacology)
AB A series of regioisomeric derivs. of a 1-methylindole-4,7-dione were synthesized, substituted with a 2-acetoxybenzoate leaving group linked through the (indol-2-yl)methyl or (indol-3-yl)methyl (or propenyl) positions. Reductive elimination of the leaving group occurred from the (indol-3-yl)methyl derivs. but not the 2-substituted regioisomers, indicating that only the C-3 position may be utilized in bioreductively-activated drug delivery, which was demonstrated with an aspirin prodrug.
ST indolequinone prodrug redn aspirin release hypoxia; drug targeting hypoxia indolequinone prodrug redn
IT Reduction
(biol.; regiospecific elimination of aspirin from reduced indolequinone prodrugs for targeting hypoxic tissues)
IT Drug delivery systems
(prodrugs; regiospecific elimination of aspirin from reduced indolequinone prodrugs for targeting hypoxic tissues)
IT Drug targeting
Hypoxia, animal
Structure-activity relationship
(regiospecific elimination of aspirin from reduced indolequinone prodrugs for targeting hypoxic tissues)
IT 113194-74-4 192820-71-6 221627-60-7 221627-61-8 221627-62-9 221627-63-0
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(regiospecific elimination of aspirin from reduced indolequinone prodrugs for targeting hypoxic tissues)
IT 50-78-2, Aspirin 221627-64-1 221627-65-2
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)

(regiospecific elimination of aspirin from reduced indolequinone prodrugs for targeting hypoxic tissues)

RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L93 ANSWER 5 OF 11 HCAPLUS COPYRIGHT 2003 ACS

AN 1999:5866 HCAPLUS

DN 130:204576

TI **Bioreductive therapies**: an overview of drugs and their mechanisms of action

AU **Rauth, A. M.**; Melo, T.; Misra, V.

CS Division of Experimental Therapeutics, Ontario Cancer Institute and Department of Medical Biophysics, University of Toronto, Toronto, ON, M5G 2M9, Can.

SO International Journal of Radiation Oncology, Biology, Physics (1998), 42(4), 755-762
CODEN: IOBPD3; ISSN: 0360-3016

PB Elsevier Science Inc.

DT Journal; General Review

LA English

CC 1-0 (Pharmacology)

AB A review with 72 refs. Bioreductively activated drugs have been used as antimicrobials, chemotherapeutic agents, and radiation sensitizers. The present paper is an overview of their mechanism of action and application in the treatment of cancer. Drugs such as nitroimidazoles, mitomycins, and benzotriazine di-N-oxides were a focus of this research. Studies have ranged from the chem. of the reductive process of activation to in vitro and in vivo studies in rodent and human cells, through to clin. testing. The variety of techniques and test systems brought to bear on these compds. is a strength of this field of research. A detailed chem. understanding of the mechanism of action of a variety of bioreductives is now available. The enzymic processes by which these drugs are activated and the cofactors involved in this activation are becoming well understood. Recent advances have been made in the design and use of dual-function bioreductives, bioreductive triggers of drug activation, and DNA-targeted bioreductives. Significant success has been demonstrated clin. with bioreductive drugs, used in combination with radiation and front-line chemotherapeutic agents. The areas of antibody-directed enzyme prodrug therapy (ADEPT) and gene-directed enzyme prodrug therapy (GDEPT) are identified as new directions for bioreductive therapy. The use of bioreductively-activated drugs for the treatment of cancer has made steady progress. The success obtained clin. and the new mol. approaches currently being implemented promise significant advances in the future.

ST review cancer bioreductive therapy

IT Antitumor agents
(bioreductive therapies: an overview of drugs and their mechanisms of action)

IT Drug delivery systems
(prodrugs; bioreductive therapies: an overview of drugs and their

mechanisms of action)
RE.CNT 72 THERE ARE 72 CITED REFERENCES AVAILABLE FOR THIS RECORD
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L93 ANSWER 6 OF 11 HCAPLUS COPYRIGHT 2003 ACS
AN 1998:694228 HCAPLUS
DN 130:90057
TI Indolequinone Antitumor Agents: Correlation between Quinone Structure, Rate of Metabolism by Recombinant Human NAD(P)H:Quinone Oxidoreductase, and in Vitro Cytotoxicity
AU **Beall, Howard D.**; Winski, Shannon; Swann, Elizabeth; Hudnott, Anna R.; Cotterill, Ann S.; O'Sullivan, Noeleen; Green, Stephen J.; Bien, Richard; Siegel, David; Ross, David; Moody, Christopher J.
CS School of Pharmacy and Cancer Center, University of Colorado Health Sciences Center, Denver, CO, 80262, USA
SO Journal of Medicinal Chemistry (**1998**), **41**(**24**), **4755**-4766
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
CC 1-3 (Pharmacology)
AB A series of indolequinones bearing various functional groups has been synthesized, and the effects of substituents on the metab. of the quinones by recombinant human NAD(P)H:quinone oxidoreductase (NQO1) were studied. Thus 5-methoxyindolequinones were prepd. by the Nenitzescu reaction, followed by functional group interconversions. The methoxy group was subsequently displaced by amine nucleophiles to give a series of amine-substituted quinones. Metab. of the quinones by NQO1 revealed that, in general, compds. with electron-withdrawing groups at the indole 3-position were among the best substrates, whereas those with amine groups at the 5-position were poor substrates. Compds. with a leaving group at the 3-indolyl Me position generally inactivated the enzyme. The toxicity toward non-small-cell lung cancer cells with either high NQO1 activity (H460) or no detectable activity (H596) was also studied in representative quinones. Compds. which were good substrates for NQO1 showed the highest selectivity between the two cell lines.
ST indolequinone prepn structure oxidoreductase metab antitumor; quinone indole prepn structure metab antitumor
IT Structure-activity relationship
(antitumor; prepn., structure, metab. by recombinant human quinone oxidoreductase, and in vitro antitumor activity of indolequinones)
IT Structure-activity relationship
(metabolic degradability; prepn., structure, metab. by recombinant human quinone oxidoreductase, and in vitro antitumor activity of indolequinones)
IT Antitumor agents
Drug metabolism
(prepn., structure, metab. by recombinant human quinone oxidoreductase, and in vitro antitumor activity of indolequinones)
IT 9032-20-6, E.C. 1.6.99.2
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); BIOL (Biological study)
(prepn., structure, metab. by recombinant human quinone oxidoreductase, and in vitro antitumor activity of indolequinones)

IT 52531-40-5P 158524-85-7P 158524-95-9P 161518-24-7P 205177-88-4P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(prepn., structure, metab. by recombinant human quinone oxidoreductase, and in vitro antitumor activity of indolequinones)

IT 52531-39-2P 161518-15-6P 161518-16-7P 161518-23-6P 161518-30-5P
161518-31-6P 161518-33-8P 161518-37-2P 191846-71-6P 191846-83-0P
192820-45-4P 192820-74-9P 192820-78-3P 205177-89-5P 205177-90-8P
205177-91-9P 205177-92-0P 205177-93-1P 205177-94-2P 215458-63-2P
215458-67-6P, 1H-Indole-4,7-dione, 3-(hydroxymethyl)-1-methyl-5-(2-methyl-1-aziridinyl)-2-phenyl- 219325-64-1P 219325-65-2P 219325-66-3P
219325-67-4P 219325-68-5P 219325-69-6P 219325-70-9P 219325-71-0P
219325-72-1P 219325-73-2P 219325-74-3P 219325-75-4P 219325-76-5P
219325-77-6P 219325-78-7P 219325-79-8P 219325-80-1P 219325-81-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn., structure, metab. by recombinant human quinone oxidoreductase, and in vitro antitumor activity of indolequinones)

IT 75-55-8 100-02-7, 4-Nitrophenol, reactions 106-51-4, 1,4-Benzoquinone, reactions 151-56-4, Aziridine, reactions 33831-72-0 219325-59-4
219325-82-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn., structure, metab. by recombinant human quinone oxidoreductase, and in vitro antitumor activity of indolequinones)

IT 3189-40-0P 219325-56-1P 219325-57-2P 219325-58-3P 219325-60-7P
219325-61-8P 219325-62-9P 219325-63-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn., structure, metab. by recombinant human quinone oxidoreductase, and in vitro antitumor activity of indolequinones)

RE.CNT 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD
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L93 ANSWER 7 OF 11 HCAPLUS COPYRIGHT 2003 ACS
AN 1998:446759 HCAPLUS
DN 129:136057
TI Indolequinone Antitumor Agents: Reductive Activation and Elimination from (5-Methoxy-1-methyl-4,7-dioxoindol-3-yl)methyl Derivatives and Hypoxia-Selective Cytotoxicity in Vitro
AU **Naylor, Matthew A.**; Swann, Elizabeth; Everett, Steven A.; Jaffar, Mohammed; Nolan, John; Robertson, Naomi; Lockyer, Stacey D.; Patel, Kantilal B.; Dennis, Madeleine F.; Stratford, Michael R. L.; Wardman, Peter; Adams, Gerald E.; Moody, Christopher J.; Stratford, Ian J.
CS Gray Laboratory Cancer Research Trust, Mount Vernon Hospital, Northwood, Middlesex, HA6 2JR, UK
SO Journal of Medicinal Chemistry (**1998**), **41**(15), **2720**-2731
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
CC 27-11 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1
AB A series of indolequinones bearing a variety of leaving groups at the (indol-3-yl)methyl position was synthesized by functionalization of the corresponding 3-(hydroxymethyl)indolequinone, and the resulting compds. were evaluated in vitro as bioreductively activated cytotoxins. The elimination of a range of functional groups (carboxylate, phenol, and thiol) was demonstrated upon reductive activation under both chem. and quant. radiolytic conditions. Only those compds. which eliminated such groups under both sets of conditions exhibited significant hypoxia selectivity, with anoxic:oxic toxicity ratios in the range 10-200. With the exception of the 3-hydroxymethyl deriv., radiolytic generation of semiquinone radicals and HPLC anal. indicated that efficient elimination of the leaving group occurred following one-electron redn. of the parent compd. The active species in leaving group elimination was predominantly the hydroquinone rather than the semiquinone radical. The resulting iminium deriv. acted as an alkylating agent and was efficiently trapped by added thiol following chem. redn. and by either water or 2-propanol following radiolytic redn. A chain reaction in the radical-initiated redn. of these indolequinones (not seen in a simpler benzoquinone) in the presence of a hydrogen donor (2-propanol) was obsd. Compds. that were unsubstituted at C-2 were found to be up to 300 times more potent as cytotoxins than their 2-alkyl-substituted analogs in V79-379A cells, but with lower hypoxic cytotoxicity ratios.
ST antitumor indolequinone prepn cytotoxicity hypoxia; reductive activation antitumor indolequinone
IT Antitumor agents
Cytotoxicity
Hypoxia, animal
Reduction potential
(prepn. and hypoxia-selective cytotoxicity of indolequinone antitumor agents)

IT 161518-24-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and hypoxia-selective cytotoxicity of indolequinone antitumor agents)

IT 192820-67-0P 192820-69-2P 210578-23-7P 210578-24-8P 210578-27-1P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. and hypoxia-selective cytotoxicity of indolequinone antitumor agents)

IT 191846-79-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); BIOL (Biological study); RACT (Reactant or reagent)
(prepn. and hypoxia-selective cytotoxicity of indolequinone antitumor agents)

IT 210578-19-1P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and hypoxia-selective cytotoxicity of indolequinone antitumor agents)

IT 192820-64-7P 192820-74-9P 192820-80-7P 192820-90-9P 192820-94-3P 210578-21-5P 210578-22-6P 210578-25-9P 210578-26-0P 210578-28-2P 210578-29-3P 210578-31-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. and hypoxia-selective cytotoxicity of indolequinone antitumor agents)

IT 52535-62-3P
RL: BYP (Byproduct); PREP (Preparation)
(prepn. and hypoxia-selective cytotoxicity of indolequinone antitumor agents)

IT 88-06-2, 2,4,6-Trichlorophenol 108-95-2, Phenol, reactions 367-12-4, 2-Fluorophenol 371-41-5, 4-Fluorophenol 393-52-2, 2-Fluorobenzoyl chloride 403-43-0, 4-Fluorobenzoyl chloride 456-22-4, 4-Fluorobenzoic acid 621-42-1, 3-Acetamidophenol 1149-26-4, N-Benzyloxycarbonyl-L-valine 4909-78-8, Dimethylformamide dineopentylacetal 5728-52-9, 4-Biphenylacetic acid 7598-91-6 191846-42-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. and hypoxia-selective cytotoxicity of indolequinone antitumor agents)

IT 40963-98-2P 52535-61-2P 52535-65-6P 192820-54-5P 205177-88-4P 210578-18-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and hypoxia-selective cytotoxicity of indolequinone antitumor agents)

IT 210578-20-4P 210578-30-6P 210578-32-8P 210578-33-9P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and hypoxia-selective cytotoxicity of indolequinone antitumor agents)

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L93 ANSWER 8 OF 11 HCAPLUS COPYRIGHT 2003 ACS
AN 1997:436012 HCAPLUS
DN 127:75527
TI 2-Cyclopropylindoloquinones and Their Analogs As Bioreductively Activated Antitumor Agents: Structure-Activity in Vitro and Efficacy in Vivo
AU **Naylor, Matthew A.**; Jaffar, Mohammed; Nolan, John; Stephens, Miriam A.; Butler, Susan; Patel, Kantilal B.; Everett, Steven A.; Adams, Gerald E.; Stratford, Ian J.
CS Gray Laboratory Cancer Research Trust, Mount Vernon Hospital, Northwood /Middlesex, HA6 2JR, UK
SO Journal of Medicinal Chemistry (**1997**), **40**(**15**

), **2335**-2346
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
CC 1-3 (Pharmacology)
Section cross-reference(s): 8

AB A series of 2-cycloalkyl- and 2-alkyl-3-(hydroxymethyl)-1-methylindoloquinones and corresponding carbamates have been synthesized and substituted in the 5-position with a variety of substituted and unsubstituted aziridines. Cytotoxicity against hypoxic cells in vitro was dependent upon the presence of a 5-aziridinyl or a substituted aziridinyl substituent for 3-hydroxymethyl analogs. The activity of 5-methoxy derivs. was dependent upon the presence of a 3-(carbamoyloxy)methyl substituent. Increasing the steric bulk at the 2-position reduced the compds.' effectiveness against hypoxic cells. A 2-cyclopropyl substituent was up to 2 orders of magnitude more effective than a 2-iso-Pr substituent, suggesting possible radical ring-opening reactions contributing to toxicity. Nonfused 2-cyclopropylmitosenes were more effective than related fused cyclopropamitosenes reported previously. The redn. potentials of the quinone/semiquinone one-electron couples were in the range -286 to -380 mV. The semiquinone radicals reacted with oxygen with rate consts. 2-8.times.108 dm3 mol-1 s-1. The involvement of the two-electron reduced hydroquinone in the mediation of cytotoxicity is implicated. The most effective compds. in vitro were the 2-cyclopropyl and 5-(2-methylaziridinyl) derivs., and of these, 5-(aziridin-1-yl)-2-cyclopropyl-3-(hydroxymethyl)-1-methylindole-4,7-dione and 3-(hydroxymethyl)-5-(2-methylaziridin-1-yl)-1,2-dimethylindole-4,7-dione were evaluated in vivo. Both compds. showed antitumor activity both as single agents and in combination with radiation, with some substantial improvements over EO9 at max. tolerated doses and as single agents against the RIF-1 tumor model and comparable efficacy in the KHT tumor model.

ST cyclopropylindoloquinone analog prepn antitumor structure activity

IT Structure-activity relationship
(antitumor; prepn. and structure-activity of cyclopropylindoloquinones analogs as antitumor agents and cytotoxicity in combination with radiation against hypoxic cells)

IT Antitumor agents
Hypoxia, animal
Radiotherapy
(prepn. and structure-activity of cyclopropylindoloquinones analogs as antitumor agents and cytotoxicity in combination with radiation against hypoxic cells)

IT 191846-46-5P 191846-62-5P 191846-71-6P 191846-72-7P 191846-79-4P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. and structure-activity of cyclopropylindoloquinones analogs as antitumor agents and cytotoxicity in combination with radiation against hypoxic cells)

IT 191846-42-1P 191846-43-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and structure-activity of cyclopropylindoloquinones analogs as antitumor agents and cytotoxicity in combination with radiation against hypoxic cells)

IT 161518-24-7P 191846-47-6P 191846-48-7P 191846-57-8P 191846-58-9P
191846-59-0P 191846-60-3P 191846-63-6P 191846-64-7P 191846-65-8P
191846-66-9P 191846-67-0P 191846-68-1P 191846-73-8P 191846-75-0P
191846-80-7P 191846-81-8P 191846-82-9P 191846-83-0P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. and structure-activity of cyclopropylindoloquinones analogs as antitumor agents and cytotoxicity in combination with radiation against hypoxic cells)

IT 191846-40-9P 191846-41-0P 191846-44-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and structure-activity of cyclopropylindoloquinones analogs as antitumor agents and cytotoxicity in combination with radiation against hypoxic cells)

IT 50-07-7 114560-48-4, EO9 158046-69-6 158046-71-0 191846-29-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. and structure-activity of cyclopropylindoloquinones analogs as antitumor agents and cytotoxicity in combination with radiation against hypoxic cells)

IT 17591-06-9P 34572-28-6P 39974-94-2P 114560-11-1P 114560-12-2P
161518-23-6P 191846-30-7P 191846-31-8P 191846-32-9P 191846-33-0P
191846-34-1P 191846-35-2P 191846-36-3P 191846-37-4P 191846-38-5P
191846-39-6P 191846-45-4P 191846-49-8P 191846-50-1P 191846-51-2P
191846-52-3P 191846-53-4P 191846-54-5P 191846-55-6P 191846-56-7P
191846-61-4P 191846-69-2P 191846-70-5P 191846-74-9P 191846-76-1P
191846-77-2P 191846-78-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and structure-activity of cyclopropylindoloquinones analogs as antitumor agents and cytotoxicity in combination with radiation against hypoxic cells)

L93 ANSWER 9 OF 11 HCAPLUS COPYRIGHT 2003 ACS
AN 1996:507061 HCAPLUS
DN 125:211954
TI Nitroimidazole-based 'extruded mustards' designed as reductively activated hypoxia-selective cytotoxins
AU **Hay, Michael P.**; Denny, William A.; Wilson, William R.
CS Cancer Res. Lab., Univ. Auckland School Med., Auckland, N. Z.
SO **Anti-Cancer Drug Design (1996), 11(5**
), **383**-402
CODEN: ACDDEA; ISSN: 0266-9536
PB Oxford University Press
DT Journal
LA English
CC 1-6 (Pharmacology)
Section cross-reference(s): 28
AB A new class of nitroimidazole alkanoic acid amides, designed to extrude para-aminophenyl mustard by intramol. cyclization following redn. of the nitro group, have been prepd. and evaluated for their ability to function as bioreductively activated prodrugs. The mechanism of activation following (bio)redn. was studied using the model compds. and the related mustard analogs. However, the reduced forms of these compds. were relatively stable and not susceptible to intramol. cyclization. This is in contrast to the corresponding 2-nitrophenylalkyl amides, where the hydroxylamino or amino redn. products undergo intramol. cyclization via a tetrahedral intermediate, resulting in cleavage of the amide and release of an activated arom. mustard. One of the 2-nitroimidazole mustards (I) had 20-fold greater toxicity towards aerobic AA8 cells than RB 6145, and a 51-fold greater toxicity towards UV4 cells (which are defective in DNA cross-link repair and thus hypersensitive to crosslinking agents). The

cytotoxicity of I against AA8 cells was enhanced 3.3-fold under hypoxic conditions, but the compd. was inactive against the hypoxic subfraction of cells in KHT tumors in vivo.

ST hypoxia antitumor nitroimidazole extruded mustard prepn

IT Hypoxia
Neoplasm inhibitors
(prepn. of nitroimidazole-based extruded mustards designed as reductively activated hypoxia-selective antitumor cytotoxins)

IT Ring closure and formation
(reductive, prepn. of nitroimidazole-based extruded mustards designed as reductively activated hypoxia-selective antitumor cytotoxins)

IT 22813-32-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(nitroimidazole-based extruded mustards designed as reductively activated hypoxia-selective antitumor cytotoxins)

IT 2067-58-5P 155877-67-1P 181370-40-1P 181370-41-2P 181370-43-4P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of nitroimidazole-based extruded mustards designed as reductively activated hypoxia-selective antitumor cytotoxins)

IT 527-73-1, 2-Nitroimidazole 533-68-6, Ethyl 2-bromobutanoate 535-11-5, Ethyl 2-bromopropionate 609-12-1, Ethyl 2-bromo-3-methylbutanoate 1010-93-1 97762-32-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of nitroimidazole-based extruded mustards designed as reductively activated hypoxia-selective antitumor cytotoxins)

IT 104-94-9P 1016-40-6P 22813-46-3P 23649-34-5P 181370-08-1P
181370-09-2P 181370-10-5P 181370-11-6P 181370-12-7P 181370-13-8P
181370-14-9P 181370-15-0P 181370-16-1P 181370-17-2P 181370-18-3P
181370-19-4P 181370-20-7P 181370-21-8P 181370-22-9P 181370-23-0P
181370-24-1P 181370-25-2P 181370-26-3P 181370-27-4P 181370-28-5P
181370-29-6P 181370-30-9P 181370-31-0P 181370-32-1P 181370-33-2P
181370-34-3P 181370-35-4P 181370-36-5P 181370-37-6P 181370-38-7P
181370-39-8P 181370-42-3P 181370-44-5P 181370-45-6P 181370-46-7P
181370-47-8P 181370-48-9P 181370-49-0P 181370-50-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of nitroimidazole-based extruded mustards designed as reductively activated hypoxia-selective antitumor cytotoxins)

L93 ANSWER 10 OF 11 HCAPLUS COPYRIGHT 2003 ACS
AN 1995:176133 HCAPLUS
DN 122:132704
TI Hypoxic radiosensitizers: substituted styryl derivatives
AU **Nudelman, Abraham**; Falb, Eliezer; Odesa, Yael; Shmueli-Broide, Naomi
CS Chem. Dept., Bar Ilan Univ., Ramat Gan, 52900, Israel
SO Archiv der Pharmazie (Weinheim, Germany) (**1994**), **327**(**10**), **619**-25
CODEN: ARPMAS; ISSN: 0365-6233
DT Journal
LA English
CC 25-19 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
Section cross-reference(s): 1, 8, 27

AB Novel styryl epoxides, N-substituted styrylethanolamines, N-mono- and N,N-bis(2-hydroxyethyl)cinnamamides (analogs of the known radiosensitizers RSU-1069, pimonidazole and etanidazole) display selective hypoxic radiosensitizing activity. The styryl group, esp. when substituted by electron-withdrawing groups, was found to be bioisosteric to the nitroimidazolyl functionality. The most active deriv., (2-nitrostyryl)oxirane, displayed a sensitizer enhancement ratio of 5 relative to misonidazole.

ST hypoxic radiosensitizer styryloxirane styrylethanolamine hydroxyethylcinnamamide; cinnamamide hydroxyethyl hypoxic radiosensitizer

IT Radiosensitizers, biological
(prepn. of styryl compds. as hypoxic radiosensitizers)

IT 160913-12-2P 160913-14-4P 160913-15-5P 160913-16-6P 160913-17-7P 160913-18-8P 160913-19-9P 160913-20-2P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)

IT 160912-89-0P 160912-90-3P 160912-91-4P 160912-92-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of styryl compds. as hypoxic radiosensitizers)

IT 6388-74-5P, (4-Nitrophenyl)oxirane 20697-05-6P, (3-Nitrophenyl)oxirane 160912-87-8P 160912-97-0P 160913-05-3P 160913-09-7P 160913-10-0P 160913-11-1P 160913-13-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of styryl compds. as hypoxic radiosensitizers)

IT 66-77-3, 1-Naphthaldehyde 100-52-7D, Benzaldehyde, derivs. 6628-86-0, 5-Chloro-2-nitrobenzaldehyde 20432-35-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of styryl compds. as hypoxic radiosensitizers)

IT 2006-14-6P 16642-94-7P 56578-39-3P 113388-92-4P 120681-10-9P 123486-66-8P 160912-88-9P 160912-93-6P 160912-94-7P 160912-95-8P 160912-96-9P 160913-07-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of styryl compds. as hypoxic radiosensitizers)

IT 160912-98-1P 160912-99-2P 160913-00-8P 160913-01-9P 160913-02-0P 160913-03-1P 160913-04-2P 160913-06-4P 160913-08-6P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of styryl compds. as hypoxic radiosensitizers)

L93 ANSWER 11 OF 11 HCAPLUS COPYRIGHT 2003 ACS
AN 1989:153954 HCAPLUS
DN 110:153954
TI **Bioreductive** heterosubstituted quinone antitumor drug delivery agents
AU **Berglund, Richard Alan**
CS Univ. Massachusetts, Amherst, MA, USA
SO (1987) 291 pp. Avail.: Univ. Microfilms Int., Order No. DA8805895
From: Diss. Abstr. Int. B 1988, 49(3), 745
DT Dissertation
LA English
CC 26-1 (Biomolecules and Their Synthetic Analogs)
Section cross-reference(s): 1
AB Unavailable
ST drug delivery **bioreductive** quinone; antitumor drug delivery quinone
IT Quinones
RL: RCT (Reactant); RACT (Reactant or reagent)
(**bioreductive** delivery systems for neoplasm inhibitors contg.)
IT Neoplasm inhibitors
(**bioreductive** quinone delivery systems for)

=> fil biosis
FILE 'BIOSIS' ENTERED AT 16:37:08 ON 04 MAR 2003
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FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 26 February 2003 (20030226/ED)

=> d all

L96 ANSWER 1 OF 1 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN **1997:233091** BIOSIS
DN **PREV199799532294**
TI Tumor targeted prodrugs: Redox-activation of conformationally constrained, bioreductive melphalan prodrugs.
AU **Chikhale, P.**; Gharat, L.; Visser, P.; Brummelhuis, M.; Guiles, R.; Borchardt, R.
CS Dep. Pharm. Sci., Univ. Maryland Baltimore, Baltimore, MD 21201 USA
SO Proceedings of the American Association for Cancer Research Annual Meeting, (1997) Vol. 38, No. 0, pp. 432-433.
Meeting Info.: Eighty-eighth Annual Meeting of the American Association for Cancer Research San Diego, California, USA April 12-16, 1997
ISSN: 0197-016X.
DT Conference; Abstract
LA English
CC General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520
Enzymes - Physiological Studies *10808
Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
IT Major Concepts
Enzymology (Biochemistry and Molecular Biophysics); Pharmacology; Tumor Biology
IT Chemicals & Biochemicals
MELPHALAN; DT-DIAPHORASE; XANTHINE OXIDASE; PHOSPHATE
IT Miscellaneous Descriptors
BIOREDUCTIVE ENZYME; BIOREDUCTIVE MELPHALAN PRODRUG; CONFORMATIONALLY CONSTRAINED; DRUG DELIVERY METHOD; DT-DIAPHORASE; HYPOXIC SOLID TUMOR; LACTONE; NEOPLASTIC DISEASE; PHARMACOLOGY; PHOSPHATE BUFFER; REDOX-ACTIVATION; REDUCTION POTENTIAL; TUMOR TARGETED DRUG DELIVERY; XANTHINE OXIDASE
RN 148-82-3 (MELPHALAN)
9032-20-6 (DT-DIAPHORASE)
9002-17-9 (XANTHINE OXIDASE)
14265-44-2 (PHOSPHATE)

=> fil reg
FILE 'REGISTRY' ENTERED AT 16:51:34 ON 04 MAR 2003
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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 3 MAR 2003 HIGHEST RN 496834-05-0
DICTIONARY FILE UPDATES: 3 MAR 2003 HIGHEST RN 496834-05-0

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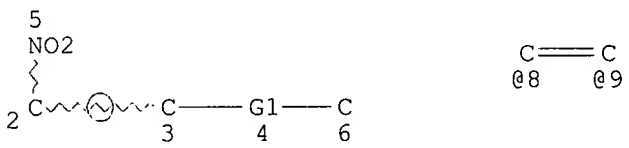
Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> d sta que l99
L97 STR



REP G1=(1-3) 8-3 9-6
NODE ATTRIBUTES:
CONNECT IS M2 RC AT 6
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 7

STEREO ATTRIBUTES: NONE
L99 3947 SEA FILE=REGISTRY SSS FUL L97

100.0% PROCESSED 7298 ITERATIONS 3947 ANSWERS
SEARCH TIME: 00.00.01

=> d his l99-

(FILE 'REGISTRY' ENTERED AT 16:37:38 ON 04 MAR 2003)
L99 3947 S L97 FUL
SAV L99 SHAR763/A

FILE 'HCAPLUS' ENTERED AT 16:42:13 ON 04 MAR 2003
L100 1859 S L99
L101 0 S L100 AND A61K047-48/IC,ICM,ICS
L102 0 S L100 AND L7-L9
L103 2 S L100 AND L5,L6
L104 427 S L100 AND (PHARMACOL? OR PHARMACEUT? OR BIOMOL?)/SC,SX
E BIOREDUCT
L105 1097 S E6-E11
L106 21 S E1,E2
E BIOREDUC
L107 54 S E4-E11
L108 0 S L100 AND L105-L107
L109 90 S L100 AND ?CONJUGAT?
L110 12 S L109 AND L104
L111 349 S L100 AND (CYCLIZ? OR CYCLIS?)
L112 76 S L111 AND L104,L109
L113 1 S L112 AND (CROHN? OR ?OSTEO? OR ?ARTHRIT?)
L114 6 S L109 AND L111
E CYCLIZATION/CT
L115 223 S E3+NT AND L100
L116 12 S L115 AND ?CONJUGAT?
L117 167 S L99 (L) (THU OR BAC)/RL
L118 3 S L117 AND L115

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L119          22 S L104 AND L115
L120           0 S L116 AND L119
L121          15 S L116,L118
L122           2 S L119 AND L117
L123          12 S L109 AND L115

     FILE 'REGISTRY' ENTERED AT 16:51:07 ON 04 MAR 2003

     FILE 'REGISTRY' ENTERED AT 16:51:34 ON 04 MAR 2003

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     (FILE 'HOME' ENTERED AT 15:04:05 ON 04 MAR 2003)
               SET COST OFF

     FILE 'HCAPLUS' ENTERED AT 15:04:46 ON 04 MAR 2003
               E WO99-GB2620/AP,PRN
L1             1 S E3,E4
               E GB98-18156/AP,PRN
L2             2 S E4
               E GB98-18030/AP,PRN
L3             1 S E4
L4             2 S L1-L3
               E THERAMARK/PA,CS
L5             5 S E3-E6
L6         35463 S ((U OR UN OR UNIV?)(L)(MANCHESTER OR VICTORIA))/PA,CS
               E FREEMAN S/AU
L7           238 S E3-E22
               E JAFFER M/AU
L8            11 S E4-E8
               E STRATFORD I/AU
L9           228 S E3-E8
               SEL RN L4

     FILE 'REGISTRY' ENTERED AT 15:10:36 ON 04 MAR 2003
L10           57 S E1-E57
L11            4 S L10 AND NITRO
L12            3 S L11 NOT PROTEINASE

     FILE 'HCAPLUS' ENTERED AT 15:12:50 ON 04 MAR 2003
L13            5 S L7-L9 AND A61K047-48/IC,ICM,ICS
L14            5 S L4,L13
L15            1 S L14 AND ?NITRO?
L16            1 S L14 AND CYCLIZAT?
L17            0 S L14 AND CYCLISAT?
L18            2 S L14 AND REDUC?
L19            3 S L14 AND BIORED?
L20            5 S L14-L19
               SEL PN APPS

     FILE 'WPIX' ENTERED AT 15:15:42 ON 04 MAR 2003
L21            7 S E58-E102
               E TI AU PA TOT
               E FREEMAN S/AU
L22           58 S E3-E14
               E JAFFER M
               E JAFFER M/AU
L23            1 S E3
               E STRATFORD I/AU
L24           18 S E3-E5
               E THERAMARK/PA
L25            5 S E3,E4
               E UYMA/PA
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                E UYMA/PACO
L26          2266 S E4,E5
                E UNIV/PA,CS
                E UNIV/PA,CSE
                E U MAN/PA
                E UN MAN/PA
                E UNI MAN/PA
                E UNIV MAN/PA
L27           140 S E4-E12
                E UNIVE MAN/PA
                E UNIVER MAN/PA
                E UNIVERS MAN/PA
                E UNIVERSI MAN/PA
                E UNIVERSIT MAN/PA
L28          2988 S A61K047-48/IC,ICM,ICS
L29            55 S A61K047-48/ICA,ICI
L30            14 S L21-L27 AND L28
L31             0 S L21-L27 AND L29
L32             2 S L30 AND ?NITRO?/BIX
L33             1 S L32 NOT ENZYME/TI
L34          3024 S L28,L29
L35             2 S L34 AND (B10-G03 OR C10-G03)/MC
L36             4 S L34 AND C07C205/IC,ICM,ICS,ICA,ICI
L37             9 S L34 AND C07D233/IC,ICM,ICS,ICA,ICI
L38            13 S L35-L37
L39            13 S L33,L38
L40           226 S (H32? OR H34? OR H36? OR H38?)/M0,M1,M2,M3,M4,M5,M6 AND L34
L41           226 S L40 AND (D? OR F? OR G?)/M0,M1,M2,M3,M4,M5,M6
L42           185 S L40 AND (M11? OR M12?)/M0,M1,M2,M3,M4,M5,M6
L43           118 S L40-L42,L39 AND A61K047-48/ICM
L44           183 S L39-L42 AND (PY<=1998 OR PRY<=1998 OR AY<=1998)
L45            87 S L44 AND A61K047-48/ICM
L46             5 S L22-L24 AND L34
L47             2 S L46 AND L40-L45
L48           172 S L44 AND (M21? OR M22? OR M23?)/M0,M1,M2,M3,M4,M5,M6
L49           158 S L48 AND (M313 OR M314 OR M315)/M0,M1,M2,M3,M4,M5,M6
L50           158 S L49 AND (M321 OR M322 OR M323)/M0,M1,M2,M3,M4,M5,M6
L51           158 S L50 AND (M331 OR M332 OR M333 OR M334)/M0,M1,M2,M3,M4,M5,M6
L52            77 S L45 AND L51
L53            20 S L52 AND B05/DC
L54            16 S L52 AND NITRO?/BIX
L55            16 S L52 AND ?NITRO?/BIX
L56           180 S L44 AND L28
L57            38 S L56 AND ?NITRO?/BIX
L58            13 S L39 AND L44
L59            49 S L33,L55,L57,L58
L60            23 S L59 AND A61K047/ICM
L61            13 S L39 AND L40-L60
L62             2 S L61 AND A61K047-48/ICM
L63            11 S L61 NOT L62
                SEL DN AN 7
L64             1 S E1-E2
L65             1 S L33 AND L21-L64
L66             2 S L64,L65
L67           807 S A61K031-04/IC,ICM,ICS,ICA,ICI
L68             5 S L67 AND L28
                SEL DN AN 4 5
L69             2 S E3-E7
L70             4 S L66,L69
L71             1 S L22-L24 AND L67
L72             2 S L22-L24 AND L39,L43
L73             5 S L70-L72
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     FILE 'WPIX' ENTERED AT 16:16:17 ON 04 MAR 2003
L74           5 S L73 AND L21-L73

     FILE 'WPIX' ENTERED AT 16:17:06 ON 04 MAR 2003

     FILE 'DPCI' ENTERED AT 16:22:17 ON 04 MAR 2003
               E GB98-18156/AP,PRN
L75           2 S E4
               E GB98-18030/AP,PRN
L76           1 S E4
               E WO99-GB2620/AP,PRN
L77           1 S E3
L78           2 S L75-L77

     FILE 'DPCI' ENTERED AT 16:23:45 ON 04 MAR 2003

     FILE 'HCAPLUS' ENTERED AT 16:24:55 ON 04 MAR 2003

     FILE 'HCAPLUS' ENTERED AT 16:25:02 ON 04 MAR 2003
               E ANTI-CANCER/JT
               E ANTI CANCER/JT
L79           1 S E4,E5 AND HAY ?/AU AND 1996/PY AND (11 AND 5 AND 383)/SO
               E INTERNATIONAL JOURNAL/JT
               E RAUTH /AU
L80           2 S E4-E10 AND BIOREDUC?/TI
L81           1 S L80 AND THERAPIES/TI
               E ARCH PHARM/JT
L82           1 S NUDELMAN ?/AU AND 1994/PY AND (327 AND 10 AND 619)/SO
L83           1 S JAFFAR ?/AU AND 1999/PY AND (9 AND 10 AND 1371)/SO
L84           1 S BEALL ?/AU AND 1998/PY AND (41 AND 24 AND 4755)/SO
L85           1 S NAYLOR ?/AU AND 1998/PY AND (41 AND 15 AND 2720)/SO
L86           1 S NAYLOR ?/AU AND 1997/PY AND (40 AND 15 AND 2335)/SO
L87           1 S EVERETT ?/AU AND 1999/PY AND (9 AND 9 AND 1267)/SO
L88           1 S PARVEEN ?/AU AND 1999/PY AND (9 AND 14 AND 2031)/SO
L89           1 S JAFFAR ?/AU AND 1999/PY AND (9 AND 1 AND 113)/SO
L90           0 S CHIKHALE ?/AU AND 1997/PY AND (38 AND 432)/SO
               E BERGLUND R/AU
L91          34 S E3,E4,E11,E12,E13,E15,E16,E20-E22
L92           1 S L91 AND BIORED?
L93          11 S L79,L81-L89,L92

     FILE 'BIOSIS' ENTERED AT 16:35:30 ON 04 MAR 2003
               E CHIKHALE P/AU
L94          24 S E3-E5
L95           4 S L94 AND 1997/PY
               SEL DN AN 4
L96           1 S E1-E2 AND L95

     FILE 'BIOSIS' ENTERED AT 16:37:08 ON 04 MAR 2003

     FILE 'REGISTRY' ENTERED AT 16:37:38 ON 04 MAR 2003
L97               STR
L98          50 S L97
L99        3947 S L97 FUL
               SAV L99 SHAR763/A

     FILE 'HCAPLUS' ENTERED AT 16:42:13 ON 04 MAR 2003
L100       1859 S L99
L101          0 S L100 AND A61K047-48/IC,ICM,ICS
L102          0 S L100 AND L7-L9
L103          2 S L100 AND L5,L6
L104        427 S L100 AND (PHARMACOL? OR PHARMACEUT? OR BIOMOL?)/SC,SX
               E BIOREDUCT
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L105        1097 S E6-E11
L106          21 S E1,E2
                 E BIOREDUC
L107          54 S E4-E11
L108           0 S L100 AND L105-L107
L109          90 S L100 AND ?CONJUGAT?
L110          12 S L109 AND L104
L111         349 S L100 AND (CYCLIZ? OR CYCLIS?)
L112          76 S L111 AND L104,L109
L113           1 S L112 AND (CROHN? OR ?OSTEO? OR ?ARTHRIT?)
L114           6 S L109 AND L111
                 E CYCLIZATION/CT
L115         223 S E3+NT AND L100
L116          12 S L115 AND ?CONJUGAT?
L117         167 S L99 (L) (THU OR BAC)/RL
L118           3 S L117 AND L115
L119          22 S L104 AND L115
L120           0 S L116 AND L119
L121          15 S L116,L118
L122           2 S L119 AND L117
L123          12 S L109 AND L115

     FILE 'REGISTRY' ENTERED AT 16:51:07 ON 04 MAR 2003

     FILE 'REGISTRY' ENTERED AT 16:51:34 ON 04 MAR 2003
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